The Feasibility of Health Technology Assessment in the Ghanaian Health System

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A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy in Health Economics

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Certificate of originality

I, Rebecca Addo, declare that this thesis is submitted in fulfilment of the requirements for the award of a Doctor of Philosophy in Health Economics, in the Business School at the University of Technology Sydney.

This thesis is wholly my own work unless otherwise reference or acknowledged. In addition, I certify that all information and literature used are indicated in the thesis. This document has not been submitted for qualifications at any other academic institution.

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Glossary

Abbreviation	Meaning
5YPOW	5 year Program of work
AES	Adverse events
AIDS	Acquired Immunodeficiency Syndrome
ANC	Antenatal Care
AUD	Australian Dollars
BIA	Budget Impact Analysis
CET	Cost Effectiveness Threshold
CEAC	Cost Effectiveness Acceptability Curve
CHEC	Consensus on Health Economics Criteria
CHEERS	Consolidated Health Economics Evaluation Reporting Standards
CHPS	Community based Health Planning and Services
CHRPE	Committee on Human Research Publication and Ethics
DALY	Disability Adjusted Life Year
DCE	Discrete choice experiment
DHD	District Health Director or District health Directorate
DHIMS	District Health Information Management System
DVT	Deep Vein Thrombosis
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
EQ-5D	EuroQol 5 dimension scale
ER	Oestrogen receptor
EuroScan	The international information network on new and emerging health technologies
GBD	Global Burden of Disease
GCO	Global Cancer Observatory
GDP	Gross Domestic Product
G-DRG	Ghana Diagnostic Related Groupings
GHC	Ghana Cedis
GHS	Ghana Health Service
GHS-ERB	Ghana Health Service Ethical Review Board
GLOBOCAN	Global Observatory of Cancer
GNDP	Ghana National Drug Program
GNMP	Ghana National Medicines Policy
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HR	Hormone Receptor
HRD	Human Resource Database
HREC	Human Research Ethics Committee
HTA	Health Technology Assessment
HTAi	Health Technology Assessment International
IC	Incremental Cost
ICER	Incremental Cost Effectiveness Ratio
iDSi	International Decision Support Initiative
IHR	Instantaneous hazard rate
INAHTA	International Network of Agencies for Health Technology Assessment
IPDD	Integrated Personnel and Payroll Database

Abbreviation	Meaning
ISPOR	International Society of Pharmacoeconomic Outcome and Research
KATH	Komfo Anokye Teaching Hospital
KNUST	Kwame Nkrumah University of Science and Technology
LLIN	Long Lasting Insecticidal Nets
MCDA	Multi-criteria decision analysis
mg	Milligram
MOH	Ministry of Health
MOU	Memorandum of Understanding
MSD	Musculoskeletal disorders
MST	Median survival time
MTHS	Medium Term Health Strategy
NCCN	National Comprehensive Cancer Network
NHIA	National Health Insurance Authority
NHIS	National Health Insurance Scheme
NICE	National Institute for Health and Care Excellence
OPD	Outpatient Department
PASC	PICO advisory sub-committee
PE	Pulmonary embolism
PICO	Population Intervention Comparator and Outcome
PR	Progesterone receptor
PSA	Probability Sensitivity Analysis
PWS	Postmenopausal Women
QALY	Quality Adjusted Life Year
QHES	Quality of Health Economics Study
RCT	Randomised controlled Trial
RR	Relative risk
SERM	Selective oestrogen receptor modulator
SF-6D	Short form 6-dimension scale
UK	United Kingdom
USA	United States of America
USD	United States Dollars
UTS	University of Technology Sydney
VB	Vaginal bleeding
VSL	Value of statistical life
WHA	World health Assembly
WHO	World Health Organisation
WTP	Willingness to Pay
YLD	Years Lived with Disability
YLL	Years of Live Lost

Abstract

The increasing costs and demands for new health technologies, which is compounded by an increase in production, has resulted in decision makers requiring high quality evidence to prioritise and allocate resources in the health system. Health technology assessment (HTA) provides such evidence and is used worldwide mostly by developed countries. HTA use is not widespread in developing country settings due to the limited human, data and financial resources available to support it. Developing countries like Ghana are planning to introduce HTA with no evidence regarding its feasibility: which systems are available to support it, and which form of HTA is most suitable for the Ghanaian setting. This thesis sought to examine these issues and make recommendations on how Ghana can proceed.

To assess the Ghanaian health system for HTA, quantitative and qualitative methods were used to examine the current decision-making practices from the perspective of national, district and clinical decision makers. Qualitative in-depth interviews were used to assess the knowledge and attitudes of decision makers and researchers about HTA. The technical capacity of Ghana for HTA was assessed using a systematic review of economic evaluation studies in Ghana. Lastly, a case study was conducted using tamoxifen for the hormonal treatment of breast cancer among pre- and peri-menopausal women. The study was designed to assess the applicability and transferability of international data to the Ghanaian context.

The results of the research conducted for this thesis revealed that Ghanaian decision makers were open to a more efficient way of making decisions that considered not only the wellbeing of the patient, but also the economic implications of such decisions, reinforcing the importance of pursuing HTA. However, lack of resources and knowledge on HTA and politico-cultural factors were reported as potential barriers and participants made suggestions to address them. The findings also highlighted the limited human and data capacity available to conduct HTA,

which meant relying on international data. However, these data need to be transformed to be context-specific before they are suitable for use in an economic evaluation.

It was concluded that Ghana will be able to adopt HTA if and when the barriers and challenges reported in this thesis are addressed. However, in the short to medium term, it is recommended that the HTA effort in Ghana focus on appraising generic medicines and unpatented technologies. Findings from these appraisals can guide funding decisions to ensure financial sustainability of the health system.

1 INTRODUCTION

1.1 Background

The demand for healthcare around the world far exceeds the resources available to deliver it. This demand continues to increase and has been accompanied by an increase in health spending which has been attributed to advances in technology, a growing aging population and consumers' awareness of new technologies, among other explanations (2). The imbalance between the demand for and supply of healthcare necessitates the prioritisation of health interventions and subsequent rationing of health resources. Prioritisation of health interventions is not a trivial exercise since policy makers need to make such decisions in a legitimate manner that is also perceived as fair and appropriate and which results in efficient use of public resources. Priority setting is defined in this context as how decisions are made about allocation of limited health resources among competing health technologies, geographical area and population groups.

In most developing countries where all resources including those earmarked for health are severely limited, priority setting in health is reported to be implicit (3-6) and done on an ad hoc basis (3) with little consideration of effectiveness, cost effectiveness or sustainability of programs with respect to available resources. The factors influencing decision-making in these settings include: the priorities and preferences of foreign donors and lobbying pressures (4); historical norms (3-5); political considerations; geography; the needs of specific groups of patients; and types of diseases (5). This implicit method of making decisions is likely to be inefficient, resulting in sub-optimal allocation of already constrained resources. Meanwhile, most governments of these countries (including most Sub-Saharan African countries), spend

on average less than US$89 per capita per year on health in comparison to US$4,543 spent by high-income countries (7).

Economic evaluation and HTA are widely recognised as essential tools to inform decision-making in health care especially around setting priorities. Economic evaluation compares the costs and consequences of different courses of action, providing decision makers with information about the relative value of different interventions to ascertain their value for money (8). HTA is a form of assessment that not only considers the effectiveness and cost effectiveness of health technologies (in an economic evaluation) but also assesses wider implications such as financial impact on the health system, social and legal consequences (9), as well as ethical implications of the technology (10).

Due to the increasing costs of health expenditures (11) and growth in medical research and production of new technologies (12) resulting in growing concerns about possibly ineffective technologies and the widespread variation in use (13), the demand for HTA has increased relative to economic evaluation. This demand is driven by the need for high quality evidence to inform decisions on efficient allocation of health resources, uses of health technologies and their diffusion in the health system (13).

Currently, HTA is broadly used across the world by countries with different income levels for different purposes including: negotiation of prices of health technologies and cost containment (14); reimbursement of drugs; selection of benefit package under an insurance scheme (15); and development of clinical guidelines (16). However, with the notable exceptions of Mexico and Thailand that successfully use HTA to inform decision-making (15, 17, 18), the use of HTA for decision-making in developing countries is not widespread (19). This has resulted in inadequate information to guide rational policymaking (including priority setting and resource allocation) and professional decisions and practices (19). Meanwhile, the focus of HTA on

resource use makes it more relevant in these settings as it empowers decision makers by providing information on health technologies that represent value for money as well as the impact of the technology on the overall budget and long-term financial sustainability of the health system (20).

The only African countries documented by the International Network of Agencies for Health Technology Assessment (INAHTA) as having an HTA agency are South Africa and Tunisia (21) however its use in decision-making is not widespread (22), just as in other countries undocumented by INAHTA. The very limited use of HTA in developing country settings has been attributed to a lack of human resource capacity to undertake it (18), the unavailability of quality data as input for it (4, 18), and the limited resources to support it (20). Meanwhile, over the last decade, there has been recognition of the importance of HTA to inform health decision-making in developing countries. This has been supported by international bodies including the World Health Organisation (WHO), which has encouraged the use of HTA among these countries[1] (19, 23-25).

Consequently, some developing countries are exploring the use of HTA with support from organisations such as the International Decision Support Initiative (iDSi), the Bill and Melinda Gates Foundation and formerly the National Institute for Health and Care Excellence (NICE) international of the United Kingdom (UK). This support has been in the form of conducting a

[1] For instance, in 2007 during the sixtieth World Health Assembly (WHA60.29), in relation to agenda item 12.19, WHO acknowledged the need for member states and donors to contain the rising costs of health care especially through adoption of new technologies. This was to be ensured through the establishment of agencies that would oversee the prioritisation of selection and acquisition of health technologies best suited to the needs and disease burden of the population, as well as ensuring the effective use of health resources. Following this, WHO signed a memoranda of understanding (MOU) with the health technology assessment societies. The International Network of Agencies for Health Technology Assessment (INAHTA), The international information network on new and emerging health technologies (EuroScan) and Health Technology Assessment International (HTAi) on collaborations to ensure the implementation of WHA60.29. Support will be provided through capacity building and by supporting health technology initiatives in developing countries. To further demonstrate WHO's commitment to efficient use of health resources through the use of HTA for decision making, another resolution was adopted in 2014 during the sixty-seventh world health assembly, WHA67.23, to encourage member states to adopt health interventions and technology assessments in support of universal health coverage (19).

situational analysis of the country, capacity building through collaborations with other HTA bodies, and piloting HTA for a selected health technology to provide decision makers with evidence on the potential benefits HTA could offer their health systems (26-29). Such countries include Ghana, Zambia, South Africa, India, Indonesia and Vietnam.

Although the move to use HTA is in the right direction, a question worth asking is whether health systems, especially those in developing countries, are ready to conduct and use it. The answer to this question is very important, as the usefulness of HTA to any health system is highly dependent on its availability, the quality of assessment and the capacity of personnel to conduct country specific appraisals. In addition, without careful planning, design and introduction of an HTA process that suits each health system's decision-making context, its objectives are in danger of not being met and the anticipated positive changes may not be realised.

For that reason, Battista and Hodge (9) advise that before HTA can be effectively incorporated in the health decision-making system of any country, an initial assessment of the existing system of priority setting and allocation of health resources is needed to identify potential barriers to its introduction, acceptability and use. This is to ensure that systems are put in place to address these barriers in the restructuring of the health system to ensure adequate utilisation of HTA and minimise, if not avoid entirely, the hindrances to HTA use in policymaking. Other researchers have supported this suggestion (30-32). Therefore, this thesis is concerned with assessing the feasibility of using HTA in Ghana. Thus, this thesis focuses on HTA for priority setting. Subsequently, the literature review conducted and all discussions will be focused on HTA, although that does not encompass all the broader priority setting literature.

The remaining sections of this chapter present the economic framework underpinning this thesis (section 1.2), motivation for the research (section 1.3), aims of the research and approach

(section 1.4), a review of the Ghanaian health system (section 1.5) and an overview of the thesis structure (section 1.6).

1.2 Economic framework

This section describes the economic framework underpinning this thesis. One key economic concept that guides effective allocation of resources to ensure their maximisation and subsequent value for money (as seen with HTA) is the principle of opportunity cost. Under this principle, the true value of an allocated resource is the benefits that could have been derived had it been allocated to its best alternative use. That is to say, using resources to fund for example, treatment A, will result in forfeiting the benefits that could have been consumed by those who would have benefited from treatment B, had it been funded. Thus, the true value of treatment A can only be known when the value of treatment B has been considered: that is, its opportunity cost. Opportunity cost is therefore defined as the potential gain or loss when one health intervention is funded over its next best alternative or a different intervention altogether.

Evidence on the opportunity costs of health resources required for health technologies can be obtained from assessments such as economic evaluation and HTA. This thesis focuses on using HTA to evaluate the opportunity costs of health technologies. Specifically, it focuses on methods of economic evaluation and budget impact analysis.

1.3 Motivation of thesis

In Ghana, not everyone can access necessary healthcare at particular points in time due to reasons including unavailability of services, inability to afford health care, despite the existence of the predominantly 'tax-funded' National Health Insurance Scheme (NHIS) that aims to ensure access to basic healthcare services to all residents of Ghana. In addition, the quantity and type of health services available through the NHIS is dependent on the services provided

by the government under the NHIS (that is, the benefit package). The content of the NHIS benefit package is reported to be determined by factors such as prevailing health conditions in Ghana, efficacy and accessibility of health technologies, and sometimes by the costs of health technologies (such as medicines). Even though the sustained provision of these services is dependent on available resources, criteria such as the cost effectiveness and financial implications of health technologies funded under the NHIS are not considered.

This raises a major concern as the government has been struggling to financially sustain the NHIS, and health system. Financial sustainability is defined in this context as the ability of the government to generate sufficient revenue to deliver the health benefits package under the NHIS, now and in the long term, in a timely and quality manner, to all those entitled to receive it without compromising other functions of the government. This situation has resulted in a ripple effect affecting access to and quality of health services provided under the scheme, because delays in reimbursement of providers (due to lack of funding) have resulted in patients not receiving care. For example, it has been reported that the availability of pharmaceuticals and diagnostic services has been reduced (33-35). These studies also reported the insured's dissatisfaction with the quality of services provided compared to those uninsured.

These challenges suggest that decision makers should adopt more systematic and explicit approaches to decision-making. Using an HTA approach to determine the opportunity cost of resources available would empower them to make more informed choices on resource prioritisation/allocation. It would ensure maximum value for money given available resources, as well as information about the financial implications of pursuing a particular choice. Ghanaian decision makers are currently embarking on the formal introduction of HTA for health decision-making without understanding the barriers to the use of HTA in developing countries as discussed above. Prior to this, policy makers in Ghana had indicated that consideration of the cost effectiveness of an intervention was one of the most important criteria

for priority setting of health interventions in the health system in a multi-criteria decision analysis study (3, 36). However, there seems to be no evidence in published literature that demonstrates the use of cost effectiveness as a decision-making criterion in the Ghanaian health system.

Nonetheless, some steps have been taken following the initial decision of policy makers to use HTA in Ghana. Through the existing engagement of NICE international with Ghana, stakeholders visited NICE in 2014 to discuss a more efficient way of funding the NHIS. Through that visit, stakeholders learnt of HTA and expressed interest in pursuing it. Subsequently, HTA was mentioned in a new Health Bill initiated in 2015. The draft Health Bill stated that a health commission would be established with the sole objective of ensuring the quality and efficiency of health care delivery in both the government and private sectors. To achieve this objective, one of the prescribed functions of the health commission is responsibility for HTA (37). However, there are no details as to how HTA will be used for service delivery or what the role of the commission will be. The Health Bill is still being developed and has not yet been enacted.

In 2016, with financial and technical support from the iDSi, NICE international carried out a pilot HTA study on hypertension with inputs from local personnel, including researchers and policy makers, in Ghana to contribute to the standard treatment guideline that was under review at the time. The findings suggested some potential cost savings on hypertensive drugs, and were used to inform the treatment protocol for hypertension in Ghana (29). This project brought together major health stakeholders in Ghana who made a commitment to using the HTA approach. A joint HTA activity program was developed between Ghana and donor partners for 2017-2020. This program aimed to develop capacity, raise awareness about HTA and conduct additional HTA projects with technical and financial support from iDSi and other partners such

as the United Nations Development Program and Program for Appropriate Technology in Health (PATH) (29).

Subsequently, the Ghana National Medicines Policy (GNMP) was developed in 2017. It made provision for the use of HTA in the selection of essential medicines (38). The document acknowledges that HTA is not yet developed in Ghana but would be useful in identifying and choosing the most cost effective health technologies. Thus, the fourth policy objective of the new GNMP is: "*To strengthen the science and practice of HTA in support of evidence-based reimbursement decisions for the government and the NHIS*" (38). It also states that HTA appraisals "*shall be applied to evidence-informed context-based decisions on health technologies, with a focus on reimbursement decisions on new expensive vaccines, diagnostics and medicines".* The GNMP also outlines an implementation plan for HTA that includes the establishment of a national committee for HTA, setting up HTA secretariat support and drafting HTA strategy and guidelines. However, there is no clearly defined timeline for implementation.

The progress made by Ghana towards the formal incorporation of HTA in heath policy decision-making is an important step in the advancement of the Ghanaian health system. However, it still remains unclear how and when the written policy will be implemented, and what type of HTAs will be undertaken and used in Ghana. Also, the policy statement is ambiguous in the sense that HTA is not in current use; hence its focus should not be on strengthening its use, but rather on introducing the practice of HTA and putting systems in place to sustain it. As affirmed by Battista and Hodge (9), it is important that prior to the institutionalisation and formal use of HTA Ghana assesses what systems are available to support HTA, the feasibility of its adoption, and if proven feasible, what form of HTA would best suit the Ghanaian health system so that the intended benefits of HTA are realised.

Therefore, the research undertaken for this thesis seeks to assess the feasibility of introducing and using HTA to inform decision-making on the allocation of public sector resources in the Ghanaian health system by considering the available national capacity and the health system's particular characteristics, and making recommendation on how Ghana can proceed. First, existing HTA practices in other countries are reviewed to evaluate their applicability to Ghana. Second, the current health decision-making practices in Ghana are assessed to identify factors that are likely to influence the formal introduction and use of HTA in the Ghanaian health system. Finally, it explores the possibility of adopting and using HTA as a decision-making tool in the context of challenges peculiar to Ghana (and other developing countries) such as limited human capacity, paucity of local evidence from economic evaluations and limited relevant data. Using Tamoxifen for the hormonal treatment of breast cancer as a case study, the research identifies what data are available and demonstrates how they can be used in a resource-constrained country like Ghana to perform a health technology appraisal. The findings also demonstrate that clinical evidence not available in Ghana can be transferred from other settings and applied to the Ghanaian context. The critical inputs needed for the conduct, transferability and applicability of HTA are taken into consideration and strategies to overcome existing challenges are proposed.

The findings of this thesis fill an important gap in the literature, and provide useful information for decision makers in relation to the proposed HTA institutionalisation in Ghana. This thesis is particularly timely given the current state of development of the Ghanaian health system, and can inform policies that will eventually be formulated for the conduct and use of HTA. As a review of literature has not identified any similar study conducted in Ghana and Sub-Saharan African countries, the findings of this study provide a useful addition to literature on HTA especially in the Sub-Saharan African context.

1.4 Aims of and approach to thesis

The main aim of this thesis is to assess the feasibility of HTA in the Ghanaian health system. Specifically, the thesis seeks to investigate:

1. Best practices of HTA in selected health systems around the world, and their adaptability and applicability to the Ghanaian health system
2. The decision-making context and practices of the Ghanaian health system
3. The knowledge and attitude of Ghanaian decision makers and researchers towards the use of HTA
4. Available technical capacity (labour and data)
5. Transferability and generalisability of data from other countries to the Ghanaian context for HTA appraisal

Figure 1-1 presents the approach used to address the aims of this thesis. Different sets of data and methods were used in this thesis, with the aims presented in one or more chapters. Thus, each chapter addresses a study aim and is presented as a unique study with objectives, methods, findings, discussions and conclusions. To investigate aims two (Chapter 3 HTA in Ghana: Perception of health workers about the decision-making process in the health system) and three (Chapter 4 HTA in Ghana: decision-making practices, knowledge and attitude of decision makers and researchers), primary data was collected from Ghana. Primary data was also collected on resource use in breast cancer (Chapters 7, 8 and 9). Ethical approval was sought from three bodies before the research commenced. Each approval covered all aspects of the data collection. Approval was also obtained from the institutions from which the data were collected. The ethical approval bodies are:

1. Ghana Health Service Ethical Review Board (ID NO: GHS-ERC: 08/01/16)

2. The Committee on Human Research Publication and Ethics (CHRPE) of the school of medical sciences, Kwame Nkrumah University of Science and Technology (CHRPE/AP/231/16)
3. University of Technology Sydney Human Research Ethics Committee (UTS HREC REF NO – ETH16-0256)

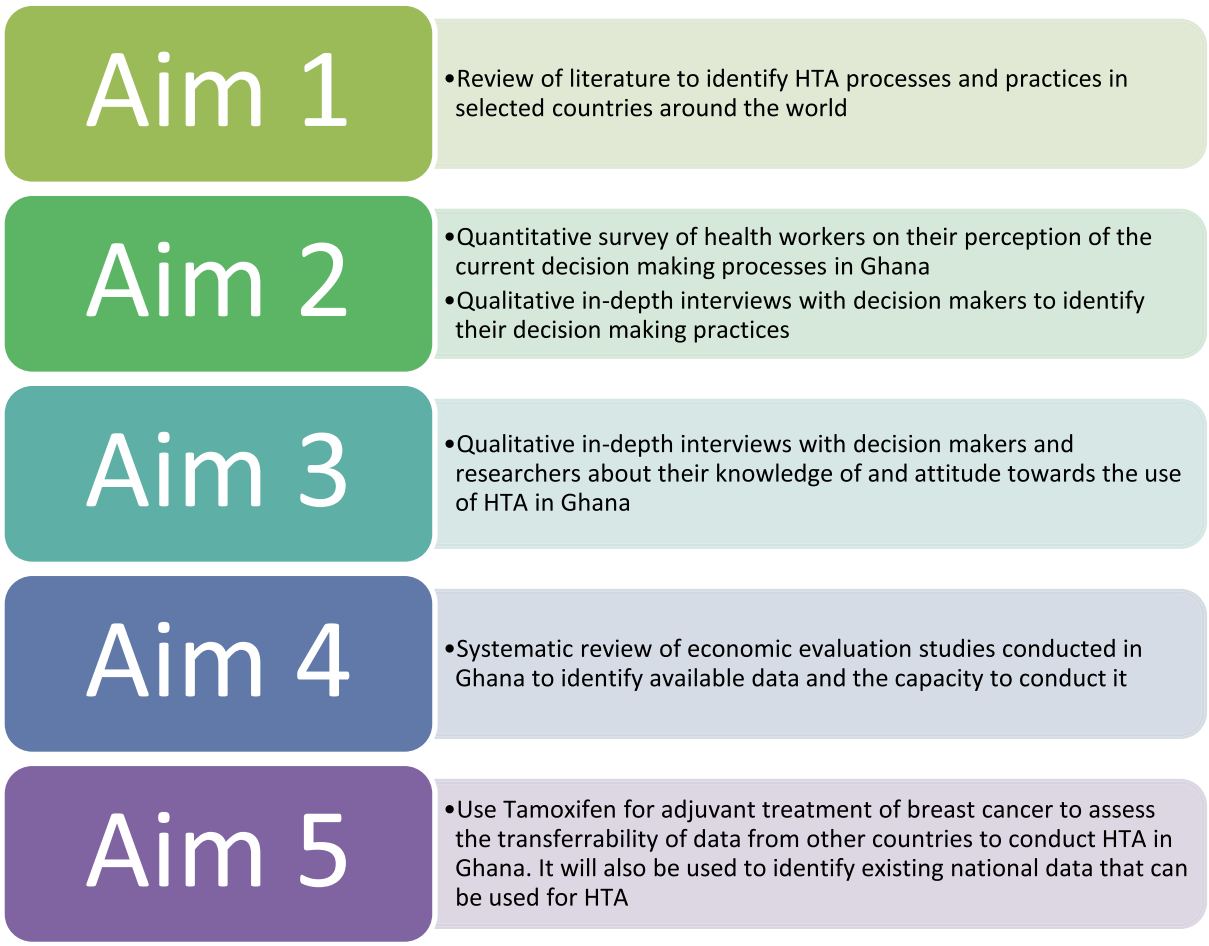


Figure 1-1: Approach to thesis

1.5 Overview of the Ghanaian health system

To understand the context in which this thesis is carried out, this section presents an overview of the Ghanaian health system to set the scene for the study.

1.5.1 National health policy

The aims of the national health policy of Ghana have been modified over the years and are currently aimed at removing financial barriers to healthcare access; improving efficiency in the health sector; reducing rates of infant, child and maternal mortalities; addressing inequities in health care distribution and access; and addressing the growing burden of non-communicable diseases. The policies are developed with contributions from major stakeholders including donor partners, and health workers at the national, regional and district levels (39-42). National health policy formation is partly driven by global agendas and directives for health systems and is invariably linked with the goal of universal health coverage (43).

The first health policy framework was developed in 1993: the Medium Term Health Strategy (MTHS) 1993-1996[2]. The overall aim of the MTHS was to improve access to health services, quality of care and efficiency of health resources; and to strengthen inter-sectoral links between health and other sectors that had direct impact on health such as Ministry of Education and Ministry of Agriculture (39).

Following the MTHS was the conception of the 5-Year Program of Work[3] (5YPOW) health policy document, of which the direction and content is derived from the MTHS. The objectives of the current 2014-2017 5YPOW are (42):

1. Bridge the equity gaps in geographical access to health services.
2. Ensure sustainable financing for healthcare delivery and financial protection for the poor.

[2] This was inspired by the overall country agenda called 'Ghana Vision 2020', a policy document developed by the National Development Planning Commission (41). Its main objective is to "consolidate the gains achieved over the past decade by the economic recovery program and lay strong foundations for accelerated growth and development in the subsequent two decades into the 21st century" (44).

[3] Program of work is a health policy document that guides the activities of the health sector for a period of five years after which it is reviewed and replaced with a new program of work. It contains the health sector objectives and activities to achieve them.

3. Improve efficiency in governance and management of the health system.
4. Improve quality of health service delivery including mental health services.
5. Enhance national capacity for the attainment of the health related Millennium Development Goals (now sustainable development goals) and sustain the gains.
6. Intensify prevention and control of non-communicable and communicable diseases.

1.5.2 Disease burden and health outcomes

Malaria remains the main cause of morbidity and mortality among Ghanaians. The prevalence of malaria per 100,000 population increases each year (45). The case fatality rate for malaria has seen a general decline though this has been inconsistent; while a decline was seen in some years, there was a rise in other years. For example, the case fatality rate for malaria in years 2007, 2008 and 2009 were 2.1, 1.4, and 1.6 respectively (45). Upper respiratory tract infection, diarrheal diseases, skin diseases, hypertension and home/occupational injuries follow malaria in terms of causes of morbidity in Ghana. Sixteen out of the top 20 causes of outpatient morbidity are preventable non-communicable diseases. The top ten causes of deaths at all ages in descending order are malaria, HIV/AIDS related conditions, anaemia, cerebro-vascular accident, pneumonia, septicemia, hypertension, cardiac diseases, meningitis, diarrheal diseases and other causes, all of which are preventable (45).

In spite of Ghana's continuous battle with preventable diseases, it has experienced a remarkable improvement in the health status indicators since 1990 (46). However, when compared with other low-middle-income countries (LMIC) and the global indicators, there is still room for improvement, as presented in Table 1-1. On the other hand, in comparison to the Africa region, Ghana is doing better.

Table 1-1: Health Status Indicators of Ghana

Indicator	Ghana		Africa		LMIC		Global	
	1990	2013	1990	2013	1990	2013	1990	2013
Life expectancy at birth (years)	57	63	50	58	59	66	64	71
Life expectancy at age 60 (years)	16	17	15	17	16	17	18	20
Healthy life expectancy at birth (years)	-	54		50		57		62
Neonatal mortality rate (per 1000 live births)	40	29	44	31	44	27	32	20
Infant mortality rate (probability of dying by age 1 per 1000 live births)	80	49	105	60	82	44	63	34
Under five mortality rate (probability of dying by age 5 per 1000 live births)	128	78	173	90	118	59	90	46

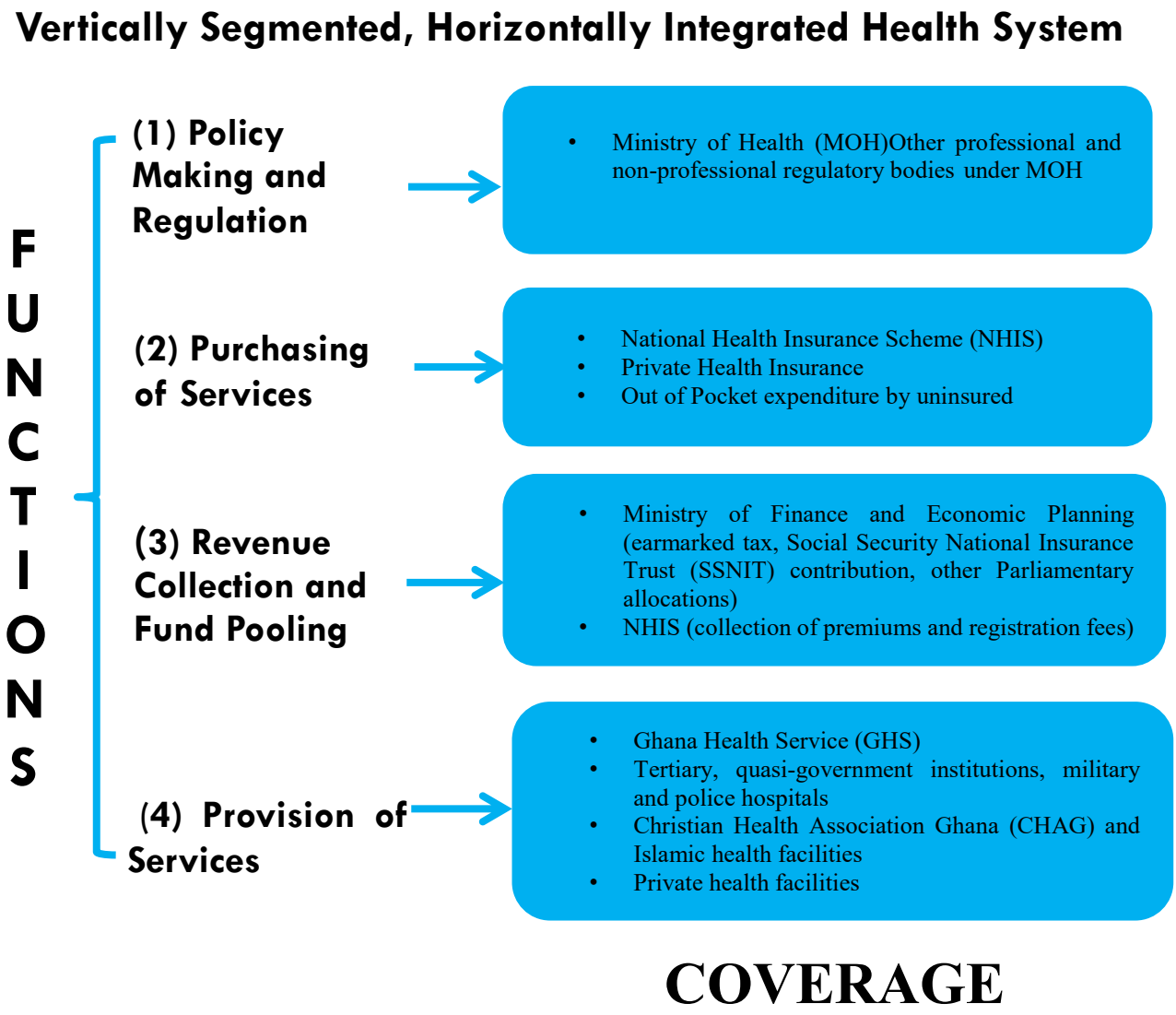
Source: World Health Statistics 2015

1.5.3 Health system design

Over the past four decades, reforms to the Ghanaian health sector have been made to improve health outcomes, protect citizens financially and ensure a responsive, efficient, equitable and sustainable health system. The reforms have resulted in separation of the three prominent functions of the health system; provision of service, financing and stewardship (policymaking and regulatory functions) (47). Murray and Frenk (48) propose that in every health system, there is either a vertical and horizontal integration or segmentation of three functions of the health system: stewardship, financing, and provision, which affects its performance. The fourth function is revenue collection and fund pooling. Where vertical represents the organisation undertaking the function and horizontal represents the population covered, examples of these are vertical and horizontal integration; vertical integration, horizontal segmentation; vertical segmentation; horizontal integration; and vertical and horizontal segmentation. Adapting[4] the model proposed by Murray and Frenk (48), the Ghanaian health system design can be described as vertically segmented and horizontally integrated as shown in Figure 1-2. As a vertically segmented health system, each of the functions of the system is performed by a separate

[4] In this thesis, stewardship from Murray and Frenk's model is represented by policymaking and regulation. It is worthy to note that Murray and Frenk defined stewardship as the activities of the body that is responsible for policymaking and regulation in the health system.

organisation/entity, whereas as horizontally integrated, they work together to cover the same population.



Note: The functions of the health system are segmented (separate from each other), while their functions work together to cover the same population (that is, horizontally integrated)

Figure 1-2: The Ghana health system model/design

Policymaking and regulation

The Ministry of Health (MOH) provides the overall policy direction for all stakeholders in the delivery of healthcare; mobilises and allocates resources to providers of health services; provide regulatory framework for all providers; and monitors and evaluates health services in

Ghana. In addition to these, the Ministry also oversees and coordinates the activities of professional bodies that regulate the training of health professionals' agencies, providers and partners in the health sector (49).

Purchasing of services, revenue collection and pooling of funds

The National Health Insurance Authority (NHIA) is responsible for purchasing health services through the NHIS, and financing health care in Ghana. Health services are purchased from both private and public health facilities (50). The private health facilities are in two categories; private-for-profit and private-not-for-profit/mission facilities. The latter constitute Christian and Muslim health facilities, which are headed informally by the Christian Health Association Ghana (CHAG).

Prior to the establishment of the NHIS in 2003, health care was provided for free after independence (1957) till the inception of the "cash and carry" system in 1990, where anyone seeking health care paid out of pocket before services were provided. The NHIS was established by law in response to a campaign promise by the then opposition party when they came into power. This explains the development of a very generous benefit package that reimburses more than 95% of all conditions seen at the Outpatient Departments (OPD) across the country as well as the diagnostic tests and medicines used for their treatment (51). (For details of the composition of the NHIS, including the benefit package, see Appendix 1 Table 11-1).

The NHIS is a mix of Beveridge and Bismarck (social health insurance) models of health systems together with other funding measures such as donor support. The national health insurance levy contributes most of the funding for the NHIS in Ghana. Other additional sources of health system financing are social security deductions from formal sector workers, parliamentary budgetary allocation, registration fees from formal and informal sector worker

enrolees, donor monies, interest on investment funds, road accident funds, premiums from the informal sector and workmen's compensation (52). Apart from the premiums and registration fees that are collected by the NHIA, the Ministry of Finance and Economic Planning pools revenue for funding health. To benefit from the NHIS, one needs to be enrolled through 1) registration with a token for the 'exempt'[5], with the exception of indigents and adults aged 70 years who do not pay registration fees, and 2) payment of premium and registration fee by informal sector workers before enjoying the benefits that come with it (51, 52). At the end of the year 2014, only 38% of the population was covered under the NHIS (42).

The NHIS reimburses providers (health facilities) for all the costs associated with treating an individual with a health condition (according to agreed protocol and reimbursement price) covered under the scheme. This includes the costs of consultations, diagnostics and medicines (listed on the NHIS medicines list). The NHIS uses three different provider payment mechanisms in the reimbursement of claims, all of which were introduced in different years. In the order of the first to be introduced, they are Fee-for Service, Case-mix (called the Ghana Diagnostic Related Group (G-DRG)) and Capitation. Inpatient services in every facility are reimbursed using the established G-DRG price. While capitation (currently suspended) were used to reimburse outpatient services in three regions, fee-for-service are used in the remaining regions. The fees are set by a committee set up by the MOH and NHIA and/or consulting agencies with inputs from stakeholders such as providers and civil society organisations (51). The evolution and use of the three payment mechanisms was prompted by the need to curb the rising cost of purchasing health services by the government through the NHIS (51). Yet, the costs borne by the government through the NHIS continue to escalate, with the scheme

[5] The 'exempt' represent those exempted from paying insurance premiums. They include children under 18 years, pregnant women, persons with mental disorders, adults aged 70 years and above, indigents and formal sector workers. Indigents are people who are very poor and do not have any source of sustenance as assessed by a social worker (51, 52).

currently facing financial unsustainability. There continues to be a deficit in the NHIS budget every year, because budgetary allocations and generated income is not sufficient to reimburse all claims submitted by health providers, as expenditures (including claims reimbursement) exceed revenues (50). To make up for the deficits, the NHIS relies on borrowing from financial institutions and/or additional funds made available by the government of Ghana (53). It is worthy to note that since the inception of the NHIS, the government's expenditure on health as a percentage of the gross domestic product (GDP) has not been stable nor increased over time. Rather it has experienced some volatility with contributing factors remaining unclear, however the gradual withdrawal of donor funds could be a factor. (See Appendix 1, Figure 11-1and Figure 11-2 for detailed description of government resources available for health care delivery).

Apart from the NHIS, other private insurance companies exist, and these are patronised by those in the private formal sector through their employers. There are two main types of private health insurance in the country: private mutual health insurance schemes (n=14) and private commercial health insurance schemes (n=3). These schemes have 144,625 registered members (0.5% of the population) (50). The majority of the population (61.5%) who are neither covered by the NHIS (because of their inability or refusal to register or enrol), nor private insurance companies, pay out of pocket for health care (43). The government plays a major role in the regulation and financing of health services at both private and public hospitals. For example, in support of the operations of the private sector, the government remunerates about 80% of salaries of health professionals who are employed in health facilities owned by the CHAG, the organisation of religious entities that operates private hospitals (54).

Provision of services

The Ghana Health Service (GHS) is responsible for nationwide health service delivery except for quasi-government hospitals (health institutions owned partly by the government and partly by Universities), tertiary teaching hospitals and other private hospitals. Private hospitals,

operated by religious groups (CHAG, Islamic Missions) and individually-owned facilities, constitute 62% of health facilities in Ghana. The GHS implements national policies for health delivery in the country as well as manages resources available for health delivery such as recruitment and deployment of health personnel throughout the country (54).

Health services in Ghana are provided in a three-tier system of care; primary, secondary and tertiary services. These are further organised at five levels: community, sub-district, district, regional and national. Different cadres of health personnel provide health services at each level. Primary care services, the first point of contact, is delivered at the community and sub-district levels. Secondary care services are delivered at the district and regional levels and tertiary care services are provided at the national level through teaching and psychiatric hospitals. Teaching hospitals provide specialised care and academic training as well as undertake research in medicine and other health related fields. The levels of services incorporate a gate-keeping structure to the secondary and tertiary levels through the use of a functional referral system from the lower levels through to the higher levels in an ascending order although this is not always adhered to (54). Private hospitals deliver primary and secondary services at the community, sub-district and district levels. (See Appendix 1, section 11.1.3 for a detailed description of the three-tier system of health care services, and Table 11-2 for the levels of care, services provided under each, and the category of health personnel who provides services at each level).

1.5.4 Priority setting and resource allocation

Table 1-2 presents a summary of the factors considered for priority setting and resource allocation in the Ghanaian health system. Durairaj et al. (55) reported that allocation of resources and priority setting at the regional and district levels are carried out based on disease burden and mortality patterns. Allocation of resources at the national level is undertaken using a formula including criteria for allocation influenced by the geographical or institutional size,

number of hospital beds and population of the area, infant mortality rate and distance of region or district from the national capital (56) (See Appendix 1, Table 11-3 for the formula).

Table 1-2: Criteria for resource allocation in the Ghanaian health system

Type of decision	Who makes the decision	Factors considered
Allocation of funds in the health sector (all levels and sectors)	Decision maker responsible (e.g. district health director, hospital administrator, regional health director)	Population density Geographical location Disease burden Mortality trends Availability of resources Capacity to utilise resources Donor interest Equity
Selection of services in the standard treatment guideline	Expert committee	Evidence of effectiveness Evidence of efficacy Evidence of availability Disease burden
Selection of essential medicines		
Selection of services reimbursed under the NHIS		
Selection of medicines to be listed on the NHIS medicines list		
Selection of services for the NHIS benefit package	Lack of guidelines/protocols to inform such decisions	

Other factors affecting resource allocation at the national, regional and district levels include human resource capacity at the local level, local capacity to use allocated funds, involvement of donors in the health system and equity considerations (57). Decision makers interviewed by Asante and Zwi (57) stated that resources such as medical devices were allocated to health facilities based on their human resource and local capacity to avoid wastage since resources are meant to be utilised. Further, because donors are major contributors of funds to the health system, activities that are run parallel to the health system and not under the control of the MOH result in inequitable distribution of health resources. To promote equity, some resources are earmarked for specific populations and geographical regions through political and administrative decisions of the ruling government.

Decisions on the essential health services to be provided to citizens by the government under the NHIS are made based on recommendations by experts (mostly clinicians) on what is

deemed necessary to treat common ailments of persons presenting at health facilities and in accordance with the standard treatment guidelines and essential medicines list (58-60). However, in the selection of the health interventions and medicines, while evidence on the efficacy and effectiveness is sometimes considered, their cost effectiveness or financial impact on the health systems budget is not (59, 60). The MOH appoints experts as an ad hoc committee which works for a specified period for that purpose only. Different committees with different members are formed every time this exercise occurs though some members may be included from the past committees (59, 60). Decisions on which drugs are added to the national essential medicines list as well as which drugs and medical services will be reimbursed under the NHIS are undertaken in similar ways (59, 60). (For a description of the process of selecting medicines and medical services under the NHIS, and selection of the essential medicines list, see Appendix 1, section 11.1.5)

1.5.5 Conclusion

This section has briefly described the Ghanaian health system according to the functions of policymaking and regulation, purchasing of services, revenue collection and funds pooling, and provision of services. It also presented the available literature on how priorities are set in the health system. The overview of the Ghanaian health system reveals that most decisions are made implicitly. In addition, there are some challenges that need addressing to ensure continuance and financial sustainability of the health system, especially the NHIS. Such measures may include using resource allocation/priority setting methods that considers the benefits forgone when resources are allocated to one intervention instead of the other (opportunity cost). Subsequently, methods evaluating the financial implications of decisions taken on the overall health budget and eventual sustainability of the health system need to be explored.

1.6 Overview of thesis structure

The thesis is organised in ten chapters. Chapter 2 two reviews the literature on HTA methods, uses and their applicability to the Ghanaian health system. Chapters 3-5 examine the health system to identify the support available for HTA. Chapter 6-9 demonstrates how data from elsewhere could be transformed for use in Ghana. Chapter 10 discusses and synthesises all the findings. Details of each chapter are presented below:

Chapter 2 provides an overview of HTA, its definition, uses, methods, and a summary of HTA practices in selected countries. The aim was to determine how current best practice could be applied to the Ghanaian context. This is followed by a review of evidence on the knowledge and attitudes of decision makers towards the use of HTA methods for health decision-making, as an introduction to the research reported in Chapters 3 and 4.

Chapter 3 presents the methods and results of a survey conducted in Ghana to assess the perception of clinical decision makers regarding the decision-making processes in the Ghana health system. It also describes their knowledge and/or training in economic evaluation.

Chapter 4 presents the methods and findings of qualitative in-depth interviews which were undertaken to examine the decision-making practices of Ghanaian decision makers and researchers. These interviews explored their knowledge of and attitudes towards the use of HTA in Ghana.

Chapter 5 assesses the human and data capacity to conduct HTA. This was done through a systematic review of published economic evaluation studies in Ghana.

Chapters 7, 8 and 9 report the results of empirical research that used a case study of tamoxifen for the hormonal treatment of breast cancer (HTBC) to demonstrate if HTA could be undertaken in Ghana using country specific data and those from other countries.

Chapter 6 presents justification for the selection of tamoxifen as a case study and a literature review on existing evidence on its use. A description of the identification of data required to conduct an economic evaluation of tamoxifen is also presented in this chapter.

Chapter 7 presents an economic evaluation of tamoxifen for the hormonal treatment of early breast cancer among pre- and peri-menopausal Ghanaian women. A Markov model was used to synthesise inputs obtained from the literature on the effectiveness of tamoxifen, quality of life and costs associated with its use.

Chapter 8 presents a second economic evaluation of tamoxifen for the adjuvant treatment of advanced breast cancer, also in pre-and-peri-menopausal women. The review conducted in Chapter 6 informed and justified both model structures and some inputs. In both Chapters 7 and 8, a description is provided of how data identified from other settings were transformed and used together with local data to conduct the evaluation. In both Chapters, two measures of health outcomes: quality adjusted life years (QALYs) gained and disability adjusted life years (DALYs) averted were used to assess the cost effectiveness of tamoxifen.

Chapter 9 estimates the financial impact of funding tamoxifen for the HTBC in Ghana.

Chapter 10 discusses the findings from the previous chapters and presents the policy implications of adopting and using HTA for decision-making in Ghana. Drawing from the results of the case study, recommendations are made.

2 HTA: A REVIEW OF LITERATURE ON METHODS, KNOWLEDGE AND ATTITUDE OF DECISION MAKERS

2.1 Introduction

Decision makers are increasingly using HTA in health systems around the world. In addition, there are a number of international organisations involved in supporting and promoting the use of HTA worldwide through the sharing and dissemination of information and development of methods for HTA. They include the INAHTA, Health Technology Assessment international (HTAi) and the International Information Network on New, Emerging and Obsolete Health Technologies (EuroScan International Network). Members of these organisations comprise HTA agencies, individuals, specific stakeholder groups (such as patients and consumers, health service providers and policy makers), and industry.

With the increased use of HTA in decision-making across the globe, extensive literature has been published on it. Therefore, as this thesis assesses the feasibility of using HTA in the Ghanaian health system, it is important that the reader be introduced to some key literature on HTA to contextualise this thesis. Thus, this chapter presents an overview of HTA: definition and types (section 2), general uses (section 3), and methods underpinning its use (section 4). It also draws on available literature to present a review of HTA processes in selected countries (section 5), and the attitudes of decision makers of these countries towards the use of HTA in the subsequent section. The chapter is concluded in section 6 by relating the main findings from this chapter to the Ghanaian health system and making recommendations, which sets the scene for the next chapter.

2.2 Definition and types of HTA

A number of international bodies including the INAHTA, Health Technology Assessment international (HTAi) and other partner organisations have defined HTA as: 'the systematic evaluation of the properties and effects of a health technology, addressing the direct and intended effects of this technology, as well as its indirect and unintended consequences, and aimed mainly at informing decision-making regarding health technologies' (INAHTA, HTAi HTA Glossary, n.d). The consequences evaluated include clinical, economic, ethical, legal and other social implications of the technology. Hence, the assessment is conducted by a multidisciplinary team, which includes health economists, biostatisticians and clinical epidemiologists.

Health technology is anything used in the delivery of healthcare. It includes procedures, devices, pharmaceuticals as well as the organisation of service delivery, policies and regulations that affect patient demand and access to health care and provider payment mechanisms (61). This thesis focuses on health technologies within the health system.

There are three main types of HTA as defined by the quality assurance group of INAHTA: HTA Report, Mini-HTA and Rapid Review. The defining characteristics of the types of HTA are illustrated in Figure 2-1. An HTA Report includes a comprehensive systematic literature review, or a systematic review of high-level evidence evaluating the safety and effectiveness of a technology as well as an analysis of its cost effectiveness. A Mini-HTA is a report that includes a comprehensive systematic literature review or a systematic review of high-level evidence, evaluating the safety and effectiveness of the technology. A Rapid Review is a report that usually includes a review of high-level evidence on the technology.

The type of HTA required by a decision maker will be dependent on a number of factors such as the intended use of the HTA findings, the time available to make a decision, the labour

capacity and the available data. For example, it is more practical for a decision maker from a low resource health system characterised by limited capacity and data sources to undertake a rapid review. Likewise, to provide information to a decision maker who is time-constrained, it would be reasonable to conduct a rapid review or mini-HTA.

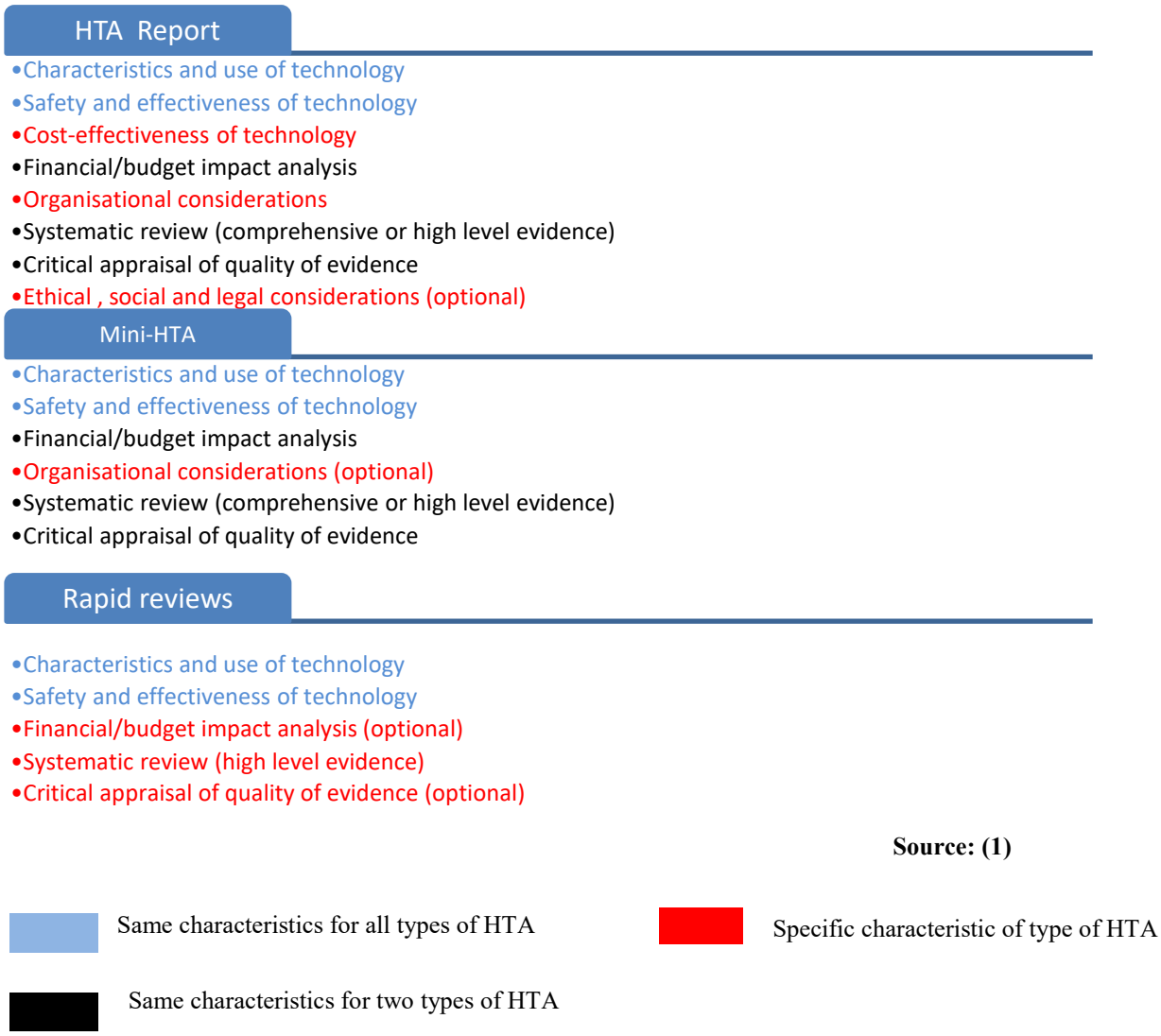


Figure 2-1: Types of HTA

2.3 Uses of HTA

HTA provides a structured approach that aids analysts in organising materials for decision makers to inform the various facets of decision-making including the effectiveness of a

technology, benefits and costs, and the social and ethical factors associated with a technology's use; as well as assessment of available alternatives (62). HTA is primarily used to determine the cost effectiveness of a technology in order to improve 'value for money' in healthcare (63). The overarching aim of HTA is to improve healthcare through influencing policy (64), and by informing decisions relating to the delivery of national, regional or local healthcare systems (65).

Table 2-1 illustrates the different types of decisions informed by HTA (1). These include regulatory approval, reimbursement to providers, procurement of equipment, product development and guidelines for treatment and support to patients. HTA agencies conduct assessments and disseminate findings to inform the above decisions. It is important to mention that different HTA agencies use varied processes for appraising health technologies and their findings are either directly linked to these decisions or otherwise. Thus, the use of HTA for health decision-making varies across governments, agencies and other health institutions. In the Ghanaian context the application of HTA could potentially inform: formulation of standard treatment guidelines, procurement of equipment, approval of new drugs, design and funding of public health programs, reimbursement of NHIS benefit packages to providers, distribution of centrally allocated resources, selection of the essential medicines list, NHIS medicines list and NHIS benefit package for health services.

Table 2-1: Uses of HTA

Organisations and individuals	Types of decisions that are informed
Government agencies, parliaments	Regulatory approval, reimbursement, public health programs, research funding
Healthcare professionals	Adoption of technologies, practice guidelines
Hospital and other healthcare administrators	Equipment procurement, availability of procedures, service delivery
Private sector insurance	Scope and extent of coverage
Manufacturing industry	Product development, marketing
Patients, carers, and their representatives	Guidance for treatment and support, access to services; shared decision-making with healthcare professionals
General public Legal professionals	Information for future decisions on healthcare Evaluate decisions after demands for the use of high cost health care technologies
Academia	Information for future healthcare professionals, decisions on research

Adopted from Hailey et al. 2014

2.4 Methods underpinning HTA

The methods and applications of HTA are broad. The methodological approach includes budget impact analysis, economic evaluations, experts opinions, qualitative analysis, post-market surveillance, clinical trials and systematic reviews, with economic evaluation being the essential component of HTA (66). The disciplines that underpin HTA are biostatistics, health economics, and epidemiology (12).

2.4.1 Economic evaluation

Economic evaluation is the systematic analysis of two or more alternative courses of action in terms of their costs and consequences, thus providing a basis for resource allocation decisions that maximise societal welfare. It also provides information about what intervention/course of action represents the best use of scarce health resources (8, 67). Economic evaluation started as a means of informing decision makers (government) on the costs and benefits associated with an intervention, particularly in instances where benefits occur in the future and other people are indirectly affected by an intervention or condition (externalities) positively or negatively (68). The costs and consequences included in the evaluation are dependent on the

perspective from which the assessment is conducted: societal, patient/family, providers, funders and health system/government. For example, whereas a funder or provider will be concerned with the costs associated with the provision of a particular health technology only, government and society more broadly may be concerned with the cost of providing the technology, the cost to other sectors and the costs incurred by patients and their families. Five main methods of economic evaluation have been described in the literature. These are cost benefit analysis, cost effectiveness analysis, cost utility analysis, cost minimisation analysis and cost consequences analysis.

Methods of economic evaluation

Cost benefit analysis (CBA)

CBA is a form of economic evaluation whereby both the costs and benefits (outcomes) are measured in monetary value. Monetary values are used because money is the conventional measure of value used in modern economies (69). Consequently, this enables comparison between the monetary returns on investments in health and that of other sectors in the economy. An advantage of this method in healthcare is that the decision maker is able to decide if a program or intervention offers society a net gain by comparing the total benefits to the total costs. If the former exceeds the latter, then the program is worth funding.

A challenge to this approach of evaluating health programs is ascribing monetary values to health outcomes. Notwithstanding this difficulty, a number of methods have been used over the years: the human capital approach, revealed preference (statistical value of life) and stated preference (commonly known as 'willingness to pay'). The human capital approach assesses health outcomes as the monetary weights placed on an individual's healthy time using the present value of the person's future earnings (70, 71). Using a revealed preferences approach, the statistical value of human life is imputed from observed data such as court judgements on

injury compensations, wage-risk studies (where individuals reveal monies they are willing to forgo to avoid a risky job) and extra pay for workers in risky occupations (70).

The last and most widely used method is the stated preference approach. This uses contingent valuation to assess individuals' preferences. The willingness to pay (WTP) method proposes that the value of health or the avoidance of illness and disease can be deduced from the amount people would be willing to pay to reduce the probability of an event such as death from a certain disease (72). However, a limitation of the WTP approach in valuing health benefits is the positive association between an individual's income and their willingness to pay; thus, this approach has received considerable criticism in regards to its use in health and other sectors of the economy (70, 73).

More recently, there has been an increase in the use of the stated preference method called discrete choice experiments (DCEs) to elicit individual preferences regarding how individuals value healthcare. DCEs allow a number of health service characteristics or factors (called attributes) to be considered in a single study (8). Such attributes can include individual preferences for take-up and acceptability of an intervention, characteristics of the program, and monetary values of the program. These attributes are combined systematically to generate a number of choice sets where an individual respondent is expected to choose between two or more alternatives presented in each choice set at a time. Therefore in choosing an alternative, individuals make a trade-off between attributes based on what is more or less important to them. Also, if monetary values are included, it is possible to estimate an individual's WTP for an intervention.

Cost effectiveness analysis (CEA)

CEA assesses the costs and effects of two or more interventions with the aim of choosing the one that maximises health outcomes. Thus, the analysis tries to identify where more

benefits/effects can be achieved at the same cost or where the least cost can be used to obtain the same benefit (67). Under CEA, health outcome measures are expressed in natural units such as deaths averted, life years gained and hospital days averted (8). CEA was first developed and used by the US military in the 1960s because it was difficult to monetise benefits. A limitation of this type of analysis is the difficulty in comparing interventions (either the same or different) evaluated with different outcome measures. Despite this limitation, its use is widespread in healthcare. It becomes exceptionally useful in most developing country settings where estimates for a common metric of measuring health outcomes (such as quality adjusted life year) are not available. Also worth mentioning is that even though CEA and subsequently cost utility analysis (CUA) do not estimate the monetary value of health benefits, decisions based on CEA or CUA consider the monetary value of health, but in a more implicit way[6]: within a WTP threshold.

Cost utility analysis

CUA is an extended version of CEA, which differs from it by using a single measure of health outcome to make a comparative value judgement between alternative health technologies. While the most common metric used for CUA is QALYs, DALYs are also used. These metrics are used to combine different types of outputs into a single measure, distinguishing it from CEA. The common metric enables a decision maker to compare an array of health technologies, allowing them to choose the ones that maximise health output within an allocated budget. While the QALYs are commonly used in developed countries, DALYs are more often used in developing countries. Even though both measures are intended for the same purpose, because each one focuses on different attributes of health (quality of life gained for QALYs and disability life years averted for DALYs), the method of estimation differs.

[6] Using a willingness to pay threshold to make decisions implies that decision-makers indirectly consider the monetary value of an intervention's costs and consequences, which is not directly captured under CEA and CUA.

QALYs

QALYs are estimated by considering both the quantity and quality of life gained through a health technology. Torrance et al. (74) introduced the concept of QALYs in the 1970s when they calculated 'health days' as the sum of the days an individual stayed healthy over a given period of time. Subsequently, its use has become widespread in the economic evaluation of healthcare and has been accompanied by a significant amount of research on the methods appropriate for estimating the quality aspect of QALYs.

Quantity of life is expressed in terms of life expectancy or survival whereas quality of life assesses different dimensions of a person's health including physical and mental health. The quality of life aspect is estimated as utility weights/values that are assigned to a particular health states (75). Utility weights range in value from 0 to 1, where 0 represents death and 1 represents perfect health. In addition, some conditions may be assessed as having a quality of life deemed to be worse than death, hence a negative value can be assigned (75, 76). There are different health states in the natural history of a disease, all of which have different symptoms and consequently, quality of life. Therefore, to obtain an accurate value for the quality of life associated with a disease state, the utilities for each health state of its natural pathway must be estimated. To obtain utilities, individuals, who may either be patients, members of the general population or health workers (experts), are asked to choose between a number of health states (via a description of each state) which may be specific to a disease or generic. In this way, individuals directly or indirectly express their preferences for health states.

In eliciting health state preferences, four main methods have been used: rating scales (also referred to as visual analogue scales), standard gamble, time trade-off (TTO) and pre-scored multi-attribute utility instruments (MAUI). In the rating scale method, individuals are asked to indicate their preference for a number of health states on a point scale (line) with two defined endpoints: for example, best and worse. Thus, the distance between the points is equivalent to

the difference in strength between the preferences assigned to each health state (77). The main weakness of this method is that individuals do not explicitly make trade-offs between health states during elicitation of their preferences, contrary to the foundations of decision theory.

The standard gamble (SG) method is considered to have the strongest theoretical foundations of choice-based valuation methods where individuals exhibit independence, completeness, transitivity and continuity in their preferences (77). In this method, individuals are asked to 'gamble' between health states that differ with respect to the probability of having the best outcome vis-à-vis the risk of the worst outcome and the certainty about a particular outcome (such as death). The probability between these choices is varied until the individual becomes indifferent. Individuals struggle to understand the concept of probabilities and this limits the SG method, as does the costs involved in undertaking it. Also, individuals' attitudes towards risk affect their responses. For instance people who are risk-averse would choose certain options such as instant death more easily leading to higher values, compared to those who are risk takers and would want to take their chances with the alternative (8, 77).

TTO methods were born out of the search for methods that could address the limitations of SG. TTO differs from SG in that the TTO has only two outcomes from which to choose, with no uncertainties or probabilities involved, while SG involves evaluating two overall 'lives' with one being certain and the other involving uncertainty (77). Under the TTO method, individuals are presented with a choice between full health for a shorter period and compromised health state for a longer period. Time spent in complete full health is varied by presenting different scenarios for the two lives until the individual becomes indifferent between the two states. It is assumed that the amount of life an individual is willing to trade-off to avoid a health state for a fixed period, which is then followed by death, is related to how much worse he/she perceives the condition to be. Thus, valuation of a particular health state will constitute trade-offs between the time spent in it and that spent in complete health. TTO is simpler to administer

compared to SG methods, even though both would require an interviewer. It is worth noting that different utility weights have been recorded among the same population using these three methods of preference elicitation (78, 79). In those studies, a greater difference was observed between outcomes for choice-based evaluation methods and the RS. Due to the similarities between TTO and SG in their methodological approach, in that both methods require respondents to make trade-offs, most guidelines for technology appraisals accept and/or recommend the use of either of them.

The pre-scored MAUI method is an alternative to eliciting preferences that bypasses the task of measuring individual preferences (as in a SG or TTO) by calculating them once with a larger sample. Due to this advantage, MAUI is widely used. It uses an existing pre-scored multi-attribute health status classification system to elicit preferences (8). The three most widely used systems are the EuroQol 5-dimension scale (EQ-5D), short form 6-dimension scale (SF-6D) and the health utilities index (HUI). While the scoring model/function for the EQ-5D was developed based on preferences elicited from the UK adult population using TTO methods, that of SF-6D and HUI were developed from preferences of the UK and Canadian adult population respectively, using SG methods. It is worth noting that these systems are different in the sense that they measure different health dimensions (some of which may overlap), each at different levels, and use different techniques to estimate the scoring formula[7]. For example, while EQ-5D has five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each with five levels of questions, SF-6D has six dimensions (physical functioning, role limitation, social functioning, pain, mental health and vitality), each with different levels of questions ranging from four to six. The mobility, pain/discomfort and

[7] Health dimensions are derived from the definition of health by the WHO that states that health is a "state of complete physical, mental and social wellbeing and nor merely an absence of a disease or infirmity". Hence, these different aspects of an individual's health are assessed by asking for a number of statements that describe using questions to rate how an individual perceives his/her health in terms of that dimensions. These statements are called levels of each dimension in a MAUI, and vary in number according to the type.

anxiety/depression dimensions of EQ-5D overlap with the physical functioning, pain and mental health dimensions of the SF-6D. Therefore, an evaluator seeking to choose a particular system should do that bearing in mind some of these characteristics. Also, in recent years, some researchers have used DCE methods to elicit the preferences of people for health states using some MAUI. For example, Oppe et al. (80) used DCEs in addition to TTO to assess individuals' preferences for health states when estimating the five dimensions of the EQ-5D.

There has been much discussion around whose preferences to elicit for estimations of utility. In the literature, preferences have been elicited from either the patient, members of the general population or 'experts' (8, 77). While it has been argued that patients are better placed to express their preferences because of their 'lived' experiences of the disease, a counter argument is that this will provide a 'false' representation of the disease, as patients adapt to their symptoms with time. Another issue with this method is the inability to elicit preferences for every disease and for conditions such as dementia and neonatal diseases because it is not possible to survey such patients.

Those who argue for experts' preferences have done so on the grounds that having the necessary knowledge about the condition puts them in a position to provide better utility estimates. However, among these three, the general population is the most preferred in taxpayer-funded health systems such as Australia and the UK, because of the notion that everyone in the general population has the potential to become a patient, hence the population are more likely to make fair choices when provided with the description of a health state. Again, as a tax or insurance payer, it is only fair that the general population be given a say in such decisions as they bear the cost of healthcare. Just like the methods of preference elicitation, differences are reported between the utilities assigned by these different types of population for a given health state and for different health conditions, which necessitate future research. For example, the utility values assigned to dementia health states by the general population was

higher than that assigned by patients with mild dementia (81). The same trend was reported in a study that assessed the quality of life due to age-related macular degenerations (82). However, in this study, utility values assigned by clinicians were also estimated and were found to be higher than that of the general population and patients for the mild form of the disease. Conversely, for moderate and severe forms of the disease, the general population utility values were higher than clinicians and patients in ascending order. On the other hand, in a different study assessing the utilities for HIV/AIDS health states, the utility values assigned by the general population were lower than those assigned by HIV/AIDS patients (83). That said, it is worth mentioning that a number of HTA agency guidelines, including NICE (84) and Pharmaceutical Benefit Advisory Committee (PBAC) (85), endorses the general public approach for market access submissions, and consequently economic evaluation.

DALYs

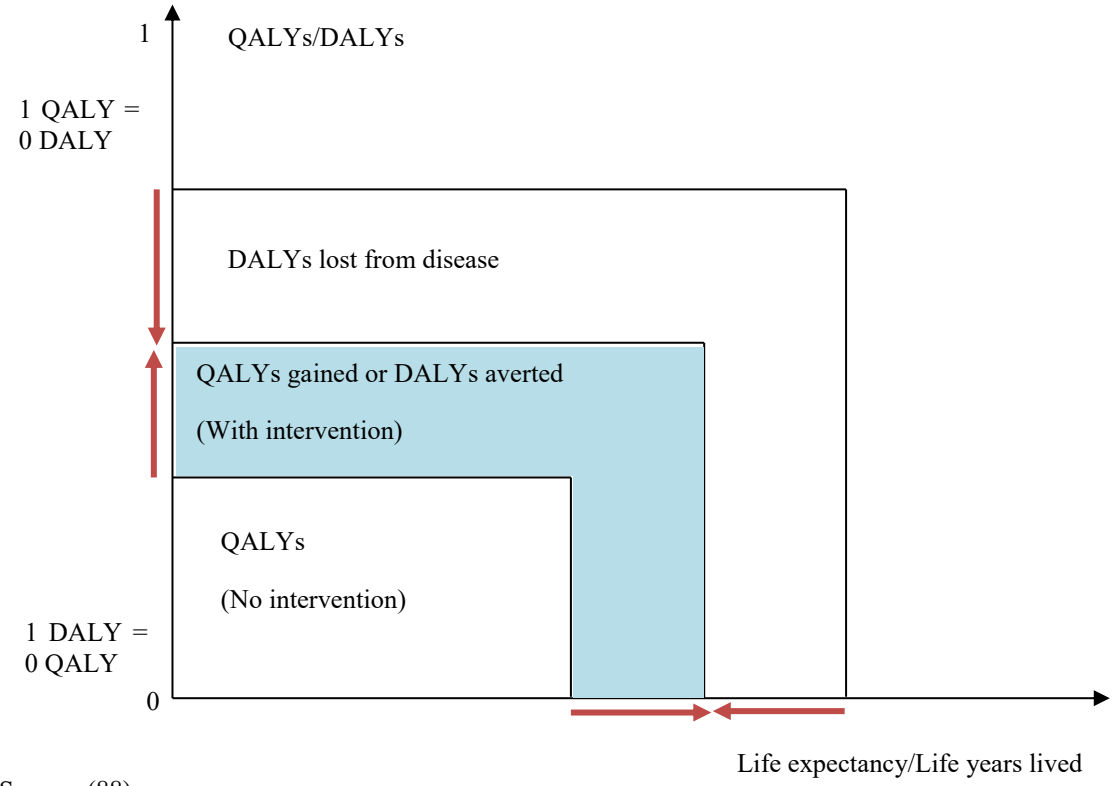
The use of DALYs became popular in the 1990s when Murray and Lopez (86) used DALYs to estimate and describe the Global Burden of Disease (GBD). They described a DALY as the sum of Years of Life Lost (YLL) and Years Lived with Disability (YLD). Murray and Lopez (86) argued that in the presence of a disease or health condition, an individual may lose life years should death occur (because the death will be premature). On the other hand, if death does not occur, the person lives with disability for the rest of his/her life or within the period the person experiences that ill-health. Hence, to appreciate the burden of any disease condition, one needs to estimate both the YLL and YLD. YLL due to premature death is estimated as the product of the number of deaths due to a condition and the life expectancy of the reference population at the time of death. YLD is also computed as the product of the prevalence of the condition and the disability weight of that condition (87).

The disability weights were initially derived from a group of experts from 60 countries who were asked to assign disability weights to 22 conditions (86), which ranged from 0 to 1, where unlike utility weights, 0 represents complete health and 1 represents death. The most current disability weights were derived from a survey of the general population of five countries. Each condition in the GBD studies has health states, each of which is assigned a disability weight (87).

The World Bank and the WHO are the organisations who mostly use DALYs as an indicator of burden of disease to make health decisions such as prioritisation of health care spending across jurisdictions and disbursement of funds within health research and developments within and across different jurisdictions. Apart from their use to measure the burden of diseases, DALYs have also been used for sectoral analysis, and in cost effectiveness analysis as an outcome measure (88).

Differences between QALYs and DALYs

Figure 2-2 illustrates the differences between DALYs and QALYs under the assumption that the quality of life under each measure was measured and valued in the same way. Here, the DALYs lost due to a disease could be considered as the converse of QALYs lived without the disease, hence DALYs averted would be equal to QALYs gained if no-one lives beyond the assumed life expectancy.



Source: (88)
Abbreviations: DALYs: disability adjusted life years; QALYs: quality adjusted life years.

Figure 2-2: Differences between DALYs and QALYs

However, this argument does not hold because the methodological approaches used in measuring and valuing DALYs and QALYs vary. Some authors have demonstrated differences between the benefits estimated for an intervention when QALYs and DALYs are used, which has policy implications. For example, Airoldi (89) showed that using DALYs and QALYs resulted in a divergence between outcomes. The number of QALYs gained were higher than the number of DALYs averted for the same intervention; the difference was attributed to the change in remaining life expectancy at different ages (that is, the use of death dependent reference age) that are used to estimate DALYs. This implies that the longer a person lives with a disability, the higher the burden, irrespective of a gain in health, unlike QALYs where the quality of life gained is solely dependent on the years of life/health gained irrespective of the age at which it occurs or the severity of disease.

Sassi (76) also confirmed the differences between these two metrics by estimating the health benefits of an intervention for non-fatal and fatal disease conditions. Just as reported by Airoldi, QALYs gained exceeded DALYs averted when the disease starts in a person's early years and lasts for a shorter duration. This also holds when the disease starts in late adulthood to older age due to the residual life expectancy. Conversely, when a disease starts in younger people, DALYs averted exceed QALYs gained. Thus, critics of DALYs have argued that it favours younger people compared to older ones irrespective of age weighting (88), which used to be factored into its calculation. Airoldi and Morton (90) recommended the use of a fixed reference age to address the differences attributed to the use of death dependent reference age (the use of life tables).

Furthermore, a recent study that evaluated the implications of using QALYs or DALYs as a measure to estimate health benefits of two preventive interventions reported that more QALYs were gained than DALYs averted in one intervention where the disease started at 11 years of age. Conversely, for the other intervention where the disease can start at any age, DALYs averted were greater than QALYs gained (91).

It is evident that the use of either DALYs or QALYs as a health outcome measure has implications for decision-making. Fox-Rushby (88) argues that QALYs are more inclusive than DALYs as they include side-effects of treatments (which are estimated as disutilities), and account for the impact of co-morbidities. She further argues that an estimate of the burden of disease (using DALYs) does not provide enough information for decision makers to allocate resources, as the opportunity cost of alternative interventions is not known. Hence, DALYs are only useful when the evaluation seeks to provide information regarding the eradication of a disease, or to ascertain the resources needed for a particular intervention. Therefore, it is not surprising that most regulatory bodies in high-income countries, where there are guidelines for conducting economic evaluation and the use of results used for funding decisions, recommend

the use of QALYs to measure health benefits. In addition, the cost effectiveness panel consisting of a panel of experts in economics, clinical medicine, statistics and ethics, with the primary aim of providing guidance to improve the quality of economic evaluations, recommended the use of QALYs to promote comparability across studies (92).

However, in the absence of locally-relevant utility weights for estimating QALYs as is the case in most developing countries, some experts have recommended DALYs as the common metric suitable for estimating health benefits because of their availability and ease of estimation using a template provided by the WHO (88, 93). In addition, as international decision makers such as the World Bank and the WHO use DALYs to compare the impact of health interventions on diseases globally and allocate funds and loans to developing countries, its use is advocated in these regions. Consequently, in 2003, the WHO employed DALYs as the outcome measure in its project 'WHO guide to cost effectiveness analysis' to conduct cost effectiveness analyses, which provided generic estimates of the cost effectiveness of a number of health interventions for use by developing countries that did not have the capacity to conduct such research. The WHO recommended its use by other analysts to aid comparability of studies (94). Furthermore, the Bill and Melinda Gates Foundation and the International Decision Support Initiative (iDSi) reference cases' for economic evaluation in developing countries, also recommend that analysts in developing countries evaluating the cost effectiveness of health technologies use DALYs as the health outcome measure (95, 96) to meet the needs of decision makers. This is a requirement for all economic evaluation studies sponsored and/or funded by the Bill and Melinda Gates Foundation to allow for comparability of results within countries and across jurisdictions for future investments. However, a counter argument to this recommendation is that even with a common measure of health outcome, comparability of results, especially in terms of cost per DALYs, across jurisdictions is inappropriate, due to differences in clinical

practice, resource availability and their subsequent use, and costs specific to each jurisdiction, which all inform the overall Incremental Cost Effectiveness Ratio (ICER).

Cost minimisation analysis (CMA)

CMA is used to compare the costs of two interventions with the same outcomes to choose the least costly alternative. Its main objective is to minimise the costs for a given outcome (73, 97). Because the analysis does not evaluate the effectiveness of the interventions under comparison, its use is only appropriate when the case for a technology has been established and the comparators are expected to have the same outcome. Even though some experts have argued that CMA is not useful compared to other methods of economic evaluations (98), the contrary is seen in practice.

In fact, its use is widespread and more applicable where market approval is being sought for technologies such as drugs. For instance, most pharmaceutical companies use CMA in market access submissions when comparing two generic drugs with the same outcome. Here, the assessor demonstrates that the two alternatives are non-inferior to each other in terms of effectiveness, but rather the difference is in the cost. HTA agencies like the PBAC of Australia accepts this form of evaluation. Indeed, due to its simplicity, CMA will also be more useful and applicable to decision makers in contexts like developing countries where there is proliferation of generic drugs, and payers are forced to pay different prices for generic drugs irrespective of their inferiority or superiority to other generic brands of same drug.

Cost consequences analysis (CCA)

In this form of analysis, the costs and consequences (outcomes) of competing interventions are estimated and presented separately without aggregating them into a single measure such as an ICER (99). Thus, in addition to health gains, outcomes such as equity, acceptability, ethical and legal implications of the intervention can be included and taken into account. An advantage

of presenting the results in this format is that the decision maker is able to choose from the costs and outcomes presented depending on what suits their context, for example resource use, to estimate the economic costs of the intervention while they consider other non-health outcomes presented to them.

On the other hand, enabling a decision maker to make these choices means leaving them to place their own value on the relative importance of different costs and benefits, thus leading to an increase in a decision maker's welfare from the economic perspective. Arguably, a decision maker making the final decision will always use a value judgement irrespective of the type of analysis. However, judging from the capacity of CCA in allowing them to 'pick and choose', a decision made using the results of such an analysis may be prone to more decision maker bias compared to the other forms of analysis.

2.4.2 Budget impact analysis (BIA)

BIA is used to estimate the financial consequences of the introduction, adoption and diffusion of a new health technology within a specific health system in the short-medium term (100). It provides estimates of how a new technology will influence health spending on the condition the technology will be used for, as well as the overall short-medium term annual budgets of decision makers both at the local and national levels. It also reveals the overall impact of adoption of the new technology on service provision (101, 102).

Whereas economic evaluation methods (except CMA) assess the cost effectiveness and efficacy of the new technology, BIA provides information on the affordability and sustainability of adopting the new technology (103). BIA thus serves as a complement to economic evaluation by providing decision makers with additional information on the allocation of scarce health resources (100, 101). One of its advantages is that it evaluates the costs of the new technology to the health system using the real target population in the setting,

and estimates its financial impact on the budget of the decision maker using a real-time horizon (varies with countries, but one to five years is acceptable) (100, 101). The financial impact is estimated based on the rate of uptake of the technology and the magnitude and timing of its impact on healthcare use and costs (102).

The emergence and development of BIA originates from the continuous development of new health technologies, the budget constraints of the health system and the inability of economic evaluation to provide information on how much it would cost the payer to fund a new technology in the short term (101). With the additional information it has to offer, it is not surprising that BIA is increasingly becoming a requirement alongside economic evaluation for HTA appraisal submissions before national or local approval for a technology to be reimbursed. Currently, countries that require BIA to be submitted alongside economic evaluation for reimbursement of new health technologies include Australia, Canada, England, Wales, Poland, Thailand, Taiwan and Belgium (15, 101, 102, 104-106).

Although the inclusion of BIA in HTA programs is gaining traction, there is a paucity of literature on its methods. The relevant available literature are mainly guidelines for its conduct, however, differences in methodologies recommended in the guidelines of various countries have been reported (101), even though they are all based on the same principle: financial impact to the budget holder. Therefore, for consistency, the International Society for Pharmacoeconomics and Outcome Research's (ISPOR) task force has reported on the principles of good practice on BIA. They recommend that methods used in BIA for new technologies take into account the necessary features of the health system, possible restrictions to access, and anticipated uptake of the new technology. They also recommend that the use and effects of current and new technologies be considered in a BIA (102) and the results be reported in a detailed manner as outlined in their guidelines.

Other researchers (105-107) also recommend BIA from the perspective of the specific healthcare decision maker or budget holder. However, the focus on the payer in a BIA underestimates the costs associated with the uptake of the technology. A full cost work-up that incorporates the costs to society, especially to the patient and family, must be considered in instances where patient and family spend directly to access the technology; these costs may hinder the uptake of the health technology. Also, where payment mechanisms are present such as co-payments and deductibles, estimating the budget impact on the users provides a complete picture of the 'true' costs of the technology. Therefore, the perspective of the BIA should be in line with the perspective of the analysis from which the health technology was evaluated and should also be broken down into the different cost bearers to facilitate easy utilisation of the results by decision makers. It is worth noting that BIA, when incorporated in HTA submissions, are briefer than those conducted as studies on their own using the ISPOR guidelines. This is because the focus of those submissions is on the effectiveness, safety and cost effectiveness of the technology under assessment. This thesis will follow the ISPOR guidelines for BIA.

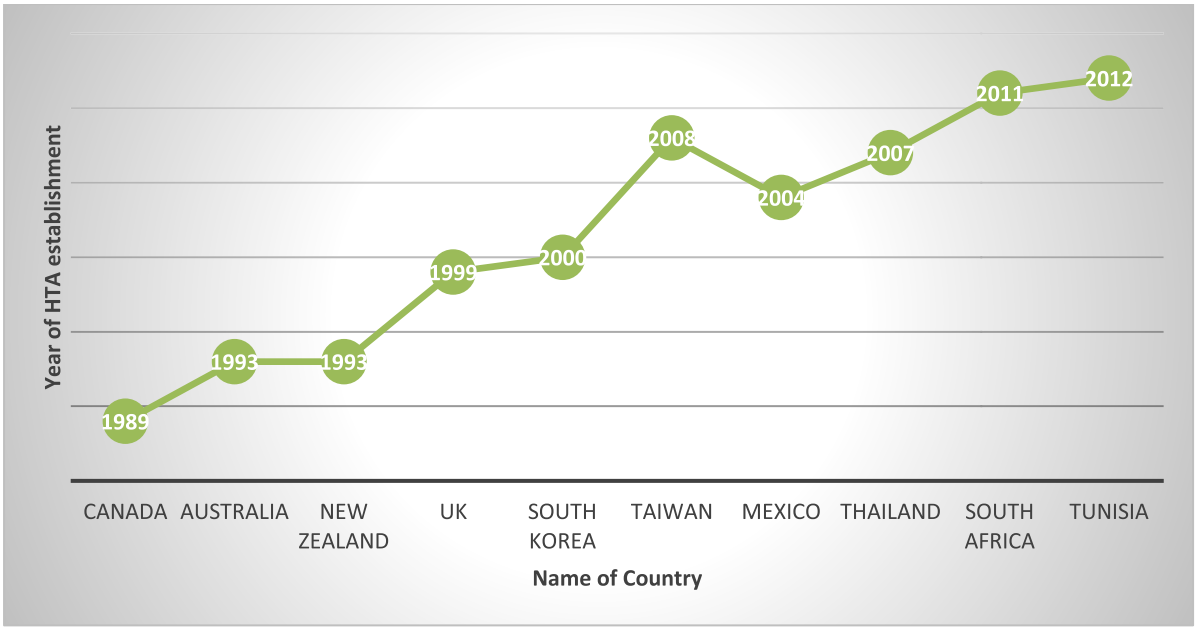
Having discussed some of the methods used in HTA, the next section presents how countries have used HTA to inform decision-making and the processes (which include methods) they use in generating such evidence.

2.5 HTA practices in selected countries

To review the HTA practices of HTA agencies around the world, ten (n=10) countries: Canada, Australia, New Zealand, UK, South Korea, Taiwan, Thailand, Mexico, South Africa and Tunisia, were conveniently selected. The criteria for selection included the income level of their population, the duration for which they have been using HTA as a technical tool to inform decision-making and the technical capacity (human and data production) available in these settings. Care was taken to select countries with varying characteristics, in terms of the criteria

set, to capture differences that could be associated with these characteristics and the application of their practices to settings with similar features. For example, Australia is a high-income country and has been using HTA for more than two decades while Thailand is a middle-income country that started using HTA about a decade ago. It is expected that these two countries will have different technical capacities, experiences and other resources such as money available for HTA that will subsequently translate into the extent to which HTA will play a role in the health system decision-making.

Figure 2-3 presents the timelines of when the selected HTA agencies were established in their respective countries. The earliest agency was instituted in 1989 in a developed country, while the latest was established in 2012 in a developing country. The establishment and use of HTA in these countries was prompted by different circumstances and contexts and for different political and health system objectives, though the overall movement for its use worldwide was driven by the rising healthcare costs and production of new technologies. As such the objectives, scope and the roles of HTA agencies differ from country to country while some common objectives such as ensuring value for money and effectiveness of technology cut across them all. While most of the triggers for the use of HTA are rising costs and cost containment in healthcare, especially under publicly financed insurance schemes (14, 108), others are concerned with reducing variations in the availability and quality of treatments and care (109).



Source: (14, 21, 104, 110-116)

Figure 2-3: Timelines for the establishment of HTA agencies

Table 2-2 presents a detailed description of HTA practices in the selected countries. The roles of HTA agencies range from carrying out technology assessment and making recommendations to informing decision-making for adoption and uptake of health technologies assessed. Health technologies assessed ranged from pharmaceuticals, medical devices and equipment, to clinical guidelines. In some countries (such as New Zealand and UK), HTA agencies have direct decision-making authority over the adoption or otherwise of technologies appraised. They are also involved in the assessment and appraisal process, whereas in other countries (such as Australia, South Korea, Canada, Mexico, Thailand, Taiwan and South Africa) a different body such as the Ministry of Health or Minister for Health makes the decision using recommendations from the HTA agency. Similarly, while for some countries (for example, UK, South Korea, Australia, and New Zealand) the outcome and recommendations of HTA are tied directly to funding decisions, in others (for example, Thailand, Mexico, South Africa, Taiwan and Canada) they are not, thus explaining the variance in the practice and uses of HTA across countries.

A number of LMIC (developing countries) have established successful HTA agencies; Thailand, Mexico, Tunisia and South Africa. In Thailand, the establishment of an HTA agency, the Health Intervention and Technology Assessment Program (HITAP) originated from the demand for economic evaluation to provide information on the effective measures for cost containment and prioritisation of health interventions under the Universal Coverage (UC) plan amidst economic recession (116). The outcome of HTA in Thailand is not directly linked to funding decisions about healthcare and services under the UC as well as the other insurance schemes available. Rather, the results are used in an advisory role in reimbursement and coverage decisions and negotiation of prices of technologies, nonetheless, there is some evidence of its influence on such decisions (113).

Similarly, the need for reliable and timely information on health technologies by decision and policy makers was the main driver of the establishment of an HTA agency in Mexico. The information provided by the agency is designed to assist decision makers to rationalise the acquisition, adoption, management and dissemination of medical technologies as well as accurate and relevant information on technologies (110). The organisation in Mexico is called the national Centre for Health Technology Excellence (CENETEC) (111). The outcome of HTA produced by CENETEC is used to inform the Ministry of Health and the General Council of Health on coverage of health technologies and priority setting for decision-making under the national health insurance system and general priority setting in the health system (110, 111).

South Africa, on the other hand, conducts HTA as translational research for effective and efficient health service delivery. The centre that conducts HTA is the Charlotte Maxeke Research Consortium (CMeRC). It was established as a collaborating agency between Charlotte Maxeke Johannesburg Academic Hospital, Gauteng Department of Health and Social Development, and the National Health Laboratory Services. Decision makers use

recommendations from these appraisals to inform their actions. In addition to advising constituent members of the group, advice is also provided to decision makers at the district and hospital levels (21).

Table 2-2: Summary of HTA processes in selected countries

HTA agency	Context under which it was established and/or aims	Scope/Focus of HTA	Process of HTA	Outcome and link to funding decisions	Uses
High-Income (developing) Countries					
Canadian Agency for Drugs and Technologies in Health (CADTH) ***Canada***	Sustainability and productivity of the health system Consumer demand for new and expensive technologies	All health technologies	Topics are identified through horizon scanning and independent submissions Works in collaboration with other academic agencies to appraise the clinical evidence, economic analysis and health services impact (BIA, population impact, planning, implementation and utilisation) of the technology	Recommendations are disseminated to all stakeholders across the nation in the form of advice HTA activity is not directly linked to funding	Informs decision makers on the clinical evidence, economic impact and health services impact of a technology to aid with their decision-making
Pharmaceutical Benefit Advisory Committee (PBAC) ***Australia***	Its primary role is to make recommendations for funding of medicines and medicinal preparations by the Australian government to ensure the delivery of a long-term fiscally sustainable health system that is safe, effective and efficient	Pharmaceuticals including vaccines	Sponsor submission Applications reviewed independently for clinical benefit, effectiveness, cost effectiveness, availability of alternative and BIA	Recommendations for listing on the Pharmaceutical Benefit Scheme (PBS)[8] Funding decisions on new and old pharmaceuticals are directly linked to HTA	Coverage and reimbursement of pharmaceuticals Revision of PBS listings for disinvestment decisions
Medical Services Advisory Committee (MSAC) ***Australia***	Its primary role is to make recommendations for funding of medical processes and procedures by the Australian government to ensure the delivery of a long-term fiscally	Medical procedures Medical processes	Submission by sponsor, and reviews done upon recommendation by the committee	Recommendations for listing on the Medical Benefit Scheme (MBS)	Coverage, and reimbursement of medical processes and procedures Disinvestment decisions

[8] The Health Minister can list a drug on the PBS without positive recommendations from evaluators.

HTA agency	Context under which it was established and/or aims	Scope/Focus of HTA	Process of HTA	Outcome and link to funding decisions	Uses
	sustainable health system that is safe, effective and efficient		Comparative safety, effectiveness and cost effectiveness and BIA	Directly determines payments to medical practitioners Indirectly determines payment for all procedures Funding decisions on new and old medical procedures and processes are directly linked to HTA	
Pharmaceutical Management Agency (PHARMAC) ***New Zealand***	Escalating costs of drugs – cost containment To ensure all citizens have best health outcomes within the available government funds	All technologies	Sponsor submission. Systematic review of CEA, BIA Conducts reviews	Has decision-making authority, hence recommendations are mandatory HTA is directly linked to funding decisions	Funding, coverage and reimbursement decisions Price negotiation Sets subsidy levels and conditions for subsidy
National Institute for Health and Care Excellence (NICE) ***UK***	To provide national guidance and advice to improve health and social care	All technologies (pharmaceuticals, medical devices and interventions, development of guidance recommendations and quality standards in social, public and clinical care)	Work commissioned by the Department of Health, submissions by sponsors Systematic review of CEA, economic analysis, BIA conducted by independent bodies Involvement of stakeholders like professional bodies, patient groups and experts	Mandatory recommendations for adoption by providers and funding by the National Health Service HTA directly linked to funding decisions	Reimbursement and coverage decisions Price negotiation and purchasing of equipment and devices Formulation of clinical, social and public health guidelines and protocols Disinvestment in old technologies

HTA agency	Context under which it was established and/or aims	Scope/Focus of HTA	Process of HTA	Outcome and link to funding decisions	Uses
					Recommendation for further research
Health Insurance Review and Assessment Service (HIRA) ***South Korea***	Funding of expensive and new technologies To curb inefficient use of health technologies For cost containment and rational use of health technologies	Medical devices and interventions Pharmaceuticals	Submissions by sponsors Reviews safety, cost effectiveness and efficacy of new technologies, economic analysis	Recommendations for coverage and funding of health technologies under the National Health Insurance Scheme HTA directly linked to funding decisions	Revision of insurance claims Coverage and reimbursement decisions Scheduling of fees and pricing of drugs
The National Institute for Health Technology Assessment (NIHTA) ***Taiwan***	Aims to reduce the burden of costs of drugs and improve efficiency in the health system Goal is to ensure the rational and efficient use of health technologies to maximise public health benefits	Pharmaceuticals Medical devices Medical interventions Policy assessments	Work is commissioned by the Ministry of Health and Welfare and other government agencies Comparative effectiveness, cost effectiveness, economic assessments and BIA	Recommendations in the form of advice	Decisions on coverage and reimbursement Disinvestment decisions concerning national health insurance reimbursed medical devices and drugs
Low and middle-income (Developing) Countries					
Health Intervention and Technology Assessment Program (HITAP) ***Thailand***	Increase in demand for expensive health technologies by consumers for inclusion on the Universal Coverage hence need for prioritisation Cost containment	Pharmaceuticals Medical devices Medical interventions Public health programs and social health policy	Submission of topics by the general public, some of which are selected during a stakeholder meeting for assessment Systematic or non-systematic review of CEA evidence, economic assessment and BIA	Recommendations in the form of advice HTA not directly linked to funding decisions	Reimbursement decisions Selection of benefit packages Negotiation of prices of technologies

HTA agency	Context under which it was established and/or aims	Scope/Focus of HTA	Process of HTA	Outcome and link to funding decisions	Uses
National Centre for Health Technology Excellence (CENETEC) ***Mexico***	To rationalise the acquisition, adoption, management and dissemination of medical technologies To provide accurate and relevant information on technologies for decision makers	Medical devices and equipment Drugs Medical and surgical procedures System management	Submission of topics by the Ministry of Health and other health institutions Safety and effectiveness; ethical, social and economic assessment	Recommendations in the form of advice HTA not directly linked to funding decisions	Priority setting Coverage of health technologies under the national health insurance system
Charlotte Maxeke Research Consortium (CMeRC) ***South Africa***	Main objective is to perform translational research for effective and efficient health service delivery	Drugs Medical devices and services Clinical practice	Evaluates the clinical, economic and social impact of use of technologies	Recommendations in the form of advice to decision makers at the national and local level HTA activity not directly linked to funding decisions	Informs decision makers on the clinical, economic and other impacts of use of the technology
National Instance for Accreditation in Health Care (INASante) **Tunisia**	The HTA mission is to give independent recommendations on a technology to support decision-making and inform allocation of resources; promote the appropriate use of health technologies; promote efficiency, safety and quality of care	Still in preparatory phase but plans to evaluate health products, professional practices, and the organisation of care and health.	Still under development	Still under development	Development of the HTA process Yet to develop capacity for HTA team

Source: (14, 21, 104, 110-118)

2.6 Review of literature on the knowledge and perception of decision makers towards the use of HTA methods/evidence for decision-making

Having described the HTA practices in these countries, this section reviews how decision makers have used its methods before and after HTA institutionalisation. Their awareness of such methods as well as perception towards their use are also explored. For the purpose of this review and thesis, knowledge is defined as having information and/or awareness of HTA evidence/methods; 'perception' is defined as how HTA methods/evidence are perceived by decision makers in terms of their importance, barriers to their use and usefulness in the health system and their daily practice. 'Use' is also defined as utilising evidence from HTA and its methods. To do this, a systematic search was conducted in databases: EMBASE, Web of Science, Econlit and PUBMED, to identify studies that reported the knowledge and perception of decision makers towards the use of HTA methods (which included economic evaluation), from January 1990 to January 2018. Keywords used for the search included "knowledge", "attitude", "perception", "decision-making", "reimbursement", "coverage decisions", "economic evaluation", "health technology assessment" and "pharmacoeconomics".

Inclusion criteria for the review were: 1) studies assessing the knowledge and attitude of decision makers and researchers towards HTA and/or economic evaluation for health decision-making, 2) studies conducted in countries where HTA agencies were reviewed under section 2.5 in addition to all studies conducted in a developing country setting[9]. Studies were excluded if they did not assess the use of HTA methods for health decision-making.

[9] Due to the limited number of HTA agencies in these countries and subsequently a little reported use of HTA methods for decision making in these settings, it was anticipated that fewer studies would be available in the study area. Hence, a decision to include all studies conducted in these settings even though the HTA agencies may not have been reviewed.

Figure 2-4 presents a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) chart for identification of papers included in the review. One thousand and forty-three (n=1043) citations were screened after removal of duplicates. Nine hundred and ninety-one (n=991) papers were excluded after screening due to reasons including that studies were not about HTA or economic evaluation (n=861) or were concerned with policy/decision-making but not the use of HTA or economic evaluation (n=40). Of the 52 studies included for eligibility screening, 19 were included in the final review after full text and/or abstract were read. The 33 studies excluded could not be assessed because their full text/abstract were not accessible (n=6), were not concerned with HTA processes (n=2), were paper reviews (n=6), were general literature on the use of evidence to make decisions (n=7) and were from countries not included in the review for this thesis (n=12).

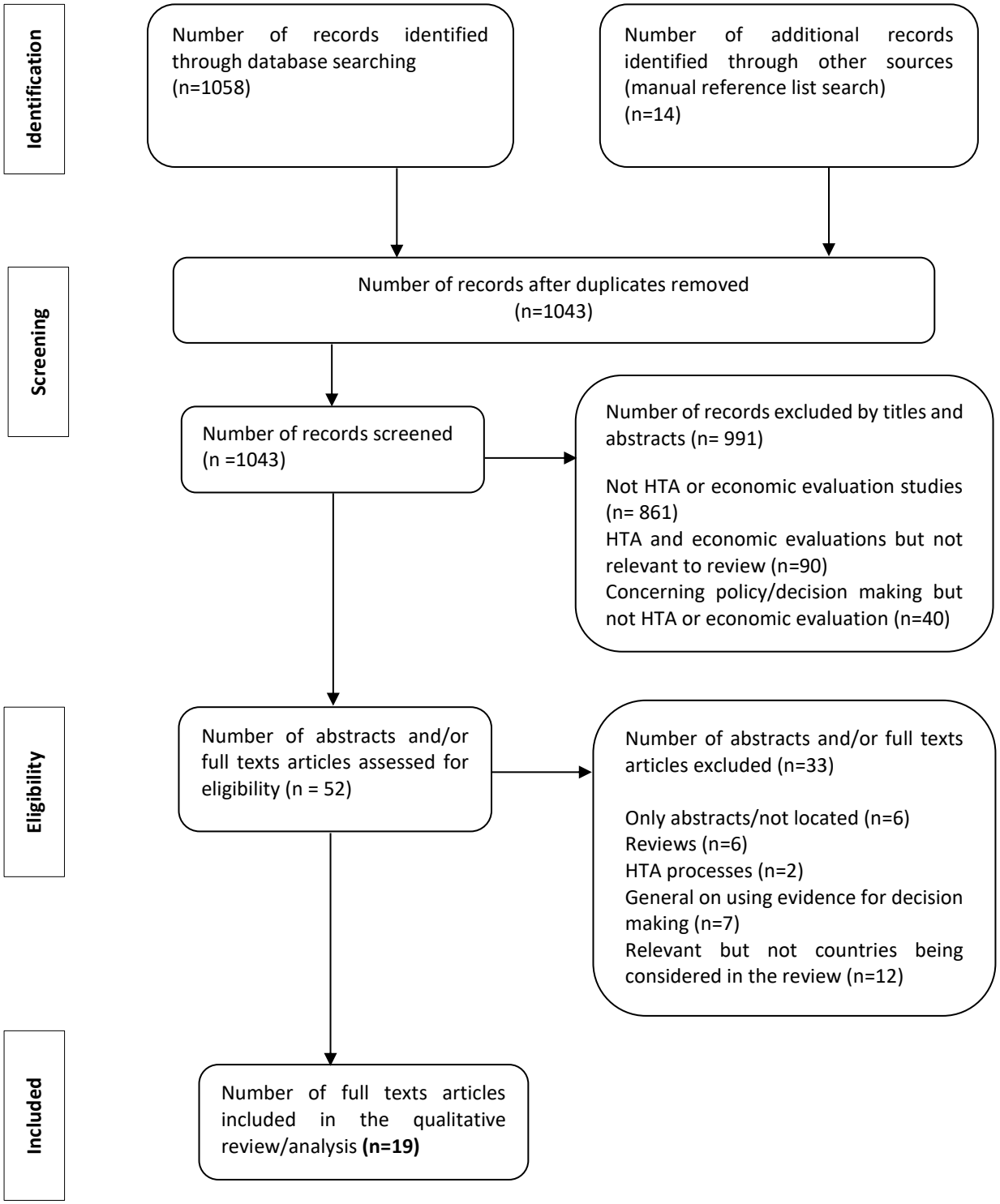


Figure 2-4: PRISMA chart illustrating the identification of studies included in the review

2.6.1 Characteristics of studies reviewed

Table 2-3 presents the characteristics of the 19 studies included in the review. Thirteen (68%) of the studies were conducted in developed countries and the remaining in developing countries. Studies conducted in developed countries were predominantly in the UK (n=9), followed by Australia (n=3) and Canada (n=1). No studies were identified from South Korea, New Zealand and Taiwan. Of the studies conducted in the UK, two (22%) were done before the formal institutionalisation of an HTA agency (NICE) to inform decision-making in 1999, one (11%) was conducted in the year of NICE's establishment and the remaining (67%) after NICE was established. All the studies identified from Australia were conducted after HTA was institutionalised; one, two years afterwards and the remaining more than 15 years after its establishment. Similarly, the study identified from Canada was conducted 16 years after CADTH was established.

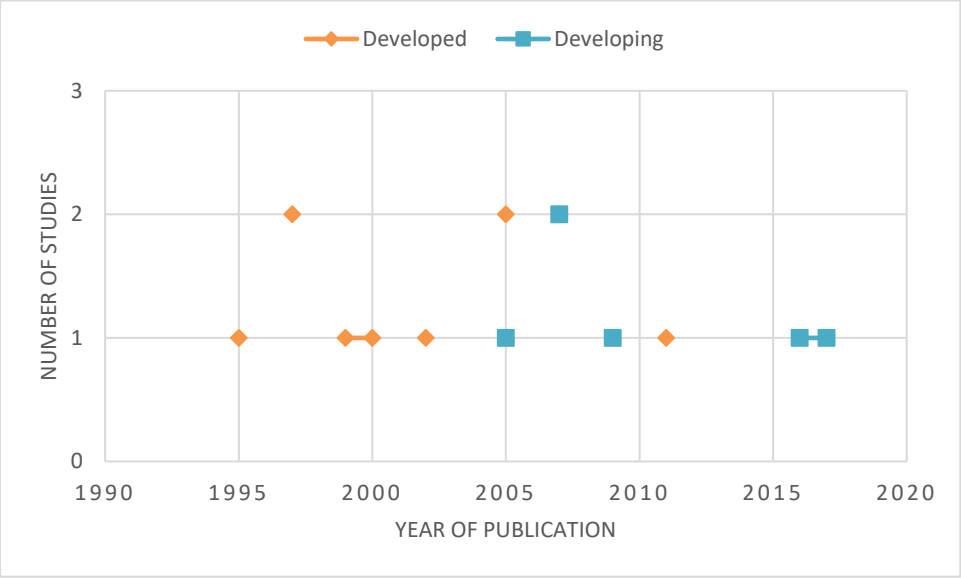
Fifty percent (50%) of studies identified from developing countries were conducted in Latin America, even though only one concerned Mexico. Thirty-three percent (33%) were conducted in Thailand and the remaining in Ethiopia. It is worthwhile to note that currently the use of any form of HTA is not formalised in Ethiopia. In addition, none of the studies were conducted on the African countries' HTA agencies that are reviewed in section 2.5 (South Africa or Tunisia). Also worth noting is the fact that all the studies conducted in developing countries were conducted prior to the formal use of any form of HTA for decision-making in the health system or just after it was introduced, such as in the case of Mexico.

Table 2-3: Characteristics of studies included in the systematic review

Study	Methods	Study population (sample size)
High-income (developed) countries		
Australia		
Ross 1995	In-depth interviews	Senior managers at the federal and state level (34)
Baghbanian, Hughes, and Khavarpour 2011	Online survey	Health administrators (91)
Gallego et al.2013	Online survey	Surgeons (62)
Canada		
Hivon et al 2005	Semi-structured interviews	Users of HTA - healthcare providers, administrators and patient associations (42)
United Kingdom		
Drummond, Cooke and Walley 1997	Postal surveys	Medical and pharmaceutical advisers, hospital directors of pharmacy and public health (446)
Walley et al. 1997	Postal survey	Primary care prescribing advisers (178)
Duthie et al. 1999	In-depth interviews	General practitioners, hospital trust representatives, health authority representatives (17 pairs)
Hoffman et al. 2000	Focus group discussion and semi-structured interviews	Representatives from government agencies and physicians (24)
Hoffman et al. 2002	Focus group discussion	Representatives from Health authorities (12)
Hasle-Phame 2005	Postal survey	Doctors and pharmacists (31)
Chen, Ashcroft and Elliot 2007	Direct observation of meetings and in-depth interviews	Medicine management committee, pharmacists (10)
Williams and Bryan 2007	Semi-structured interviews, documentary analysis and observation of committee meetings	Local committee members, including representatives of primary care trusts and NHS trusts, hospital medicine management committee (302)
Eddama and Coast 2009	In-depth interviews, direct observation of meetings, analysis of minutes from previous meetings	Local decision makers - hospital managers, primary care trust managers, palliative care managers, cancer network managers, general practitioners, clinicians, strategic health authority managers (20)
Low and middle-income (developing) countries		
Latin America		
Iglesias, Drummond and Rovira 2005 (The Latin Americas)	Open-ended postal survey	Representatives from government agencies
Rubinstein et al 2007 (Argentina)	Focus group discussion and in-depth interviews	Health secretariats, social and private insurance managers, hospital managers and clinicians (20)
Jaramillo et al. (2016) (Colombia)	In-depth semi-structured interviews	HTA researchers (5)
Thailand		
Teerawattananon and Russel (2008)	In-depth interviews	Senior policy makers at the national level, hospital directors, academics and health professionals (36)
Chaikledkaew et al. 2009	Postal survey	Researchers, members of the management committee of provincial health offices, hospital formulary drug committee members
Ethiopia		

Study	Methods	Study population (sample size)
Zegeye et al. (2017)	In-depth interviews	Healthcare managers, program coordinators and clinicians (57)

Figure 2-5 illustrates the differences in the number of studies published over the years from developed and developing countries. All the studies conducted in developing country settings were published after 2004. Conversely, most of the studies from developed countries were published before 2004 and after HTA was institutionalised, hence the formal use of such methods for decision-making.



Note: the same number of studies were conducted in both developed and developing countries in the years 2007 and 2009

Figure 2-5: Distribution of publications among developed and developing countries.

2.6.2 Context and methodological approaches used

Two main contexts were identified for the conduct of these studies: prior to the formal use of HTA in the health system and after the formal introduction of HTA to inform health decisions on the development and/or review/promotion of HTA. Studies conducted in the former were mostly from developing countries and were in anticipation of the formal use and/or institutionalisation of HTA in their health systems. Thus, these studies sought to identify potential barriers to the introduction and use of any methods of HTA. However, an exception

is seen in the studies conducted in the UK prior to institutionalisation of NICE, where some health authorities reported a limited use of HTA methods. On the other hand, studies conducted after HTA was institutionalised sought to identify the barriers to the use of HTA methods.

Both quantitative and qualitative methodological approaches were used to assess the knowledge and attitude of decision makers (and researchers in some instances) towards the use of HTA methods. Within these methodological approaches, different data collection techniques were used. For the quantitative method studies, postal and online surveys were used. The studies that used qualitative methods used either one or a combination of the following data collection techniques: in-depth interviews, semi-structured interviews, focus group discussions, direct observation of meetings and document analysis (see Table 2-3).

Table 2-3 presents the study population sampled and sample size for each article included in the review. Only three papers (2, 6, 119) sampled researchers/ academics for their studies. The most frequently sampled decision makers were physicians, pharmacists, senior policy makers, hospital managers and directors, and medicines committee members. In addition, each study sampled more than one category of decision maker as the study population.

The next two sections present an overview of study findings on the knowledge of and attitudes towards, and use of, HTA methods, and the barriers to its use as reported by decision makers interviewed/surveyed in these studies. The discussion in these sections is based on the content of these studies at the time of their publication, to answer the objective of this thesis: draw the differences between findings from different contexts. It is therefore worthwhile to note that, what was reported in these studies might have changed over the years as HTA methods have evolved, as has its diffusion and use. The concept of ensuring efficiency in the allocation of health care resources is currently widespread and accepted, hence it is expected that responses would probably vary if the same studies were conducted now.

2.6.3 Knowledge and use of HTA methods

The studies reviewed suggested that generally the use of HTA methods among decision makers were limited, in both settings where HTA was institutionalised and also where it was not. The knowledge of HTA methods were not widespread. Nonetheless, comparing the knowledge and use in both settings, its use was more widespread in settings where HTA methods were institutionalised than where it was not.

The review discovered that the limited use of HTA methods was associated with the lack of knowledge about the methods. For example, studies that reported the lack of knowledge about HTA methods, such as those carried out in developing countries among decision makers, reported a consequent non-use to inform decisions (2, 5, 6, 120, 121). In addition, the extent of use of HTA methods was associated with the presence or absence of a formal HTA agency that makes recommendations or mandates decision makers to use its findings. Such is observed among senior managers who reported using HTA methods at the federal and state level of the Australian health system because it was mandatory (122). Also in the UK, prior to the establishment of NICE, Drummond et al (123) and Walley et al (124) reported that the proportion of respondents who used HTA methods was smaller compared to those who reported having knowledge about such methods due to the lack of guidelines requiring their use. A similar situation is seen in the developing countries where the use of HTA methods was almost non-existent even though some respondents reported having some form of HTA training and knowledge of HTA methods (2, 5, 6).

Again, the roles of decision makers, respondents' exposure to HTA methods and the health system characteristics such as decision-making processes also contributed to the use or non-use of HTA methods. For instance, compared to decision makers, a greater proportion of researchers reported having knowledge of HTA (6, 119, 125). Eddama and Coast (31) also reported that even though some local decision makers had knowledge of HTA methods, and its

use were mandatory at the time of data collection, they were not using it because their roles were mostly managerial and did not involve making choices between different health technologies. The results of Ross (122) and Baghbanian et al. (126), where decision makers were not using HTA methods because they did not perceive its benefit to their decision-making roles, corroborates this.

Despite the reported limited knowledge and use of HTA methods among decision makers, there was a positive attitude towards its use. The majority of studies (89%) stated that respondents acknowledged its relevance and expressed interest in using HTA if the barriers to its use were addressed.

These findings suggest that the use of HTA methods to inform health decisions remained limited irrespective of the settings and contexts under which the studies were performed. Some of the reasons attributed to non-use include knowledge and role of decision makers, existence of a well-developed processes of decision-making (like the establishment of an HTA agency), and policies mandating HTA use. The next section describes the reported barriers to the use of HTA methods by respondents in the studies included in this review.

2.6.4 Barriers to the use of HTA methods for decision-making

Table 2-4 presents a typology of barriers reported by decision makers from each study. Barriers identified are classified into three major headings: health systems constraints, user characteristics, and conduct of and access to HTA methods.

Table 2-4: Distribution of barriers to the use of HTA methods reported by respondents/interviewees of studies reviewed

Study	Barriers to the use of HTA methods														
	Health system constraints			User characteristics				Conduct of and access to HTA methods							
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
Developed/High-income countries															
Ross 1995	√			√		√				√				√	√
Baghbanian, Hughes, and Khavarpour 2011	√	√			√					√					
Gallego et al.2013				√	√										
Hivon et al 2005	√		√	√				√							
Drummond, Cooke and Walley 1997	√	√		√						√		√			
Walley et al. 1997		√		√						√		√			
Duthie et al. 1999				√			√								√
Hoffman et al. 2000		√		√						√		√			
Hoffman et al. 2002					√					√	√				
Hasle-Phame 2005				√						√	√				
Chen, Ashcroft and Elliot 2007		√			√					√	√		√	√	
Williams and Bryan 2007					√			√		√			√		
Eddama and Coast 2009	√	√			√	√									
Developing/Low and middle-income countries															
Iglesias, Drummond and Rovira 2005								√	√		√		√		
Rubinstein et al 2007	√	√	√	√				√			√		√	√	
Jaramillo et al. (2016)	√		√					√					√		
Teerawattananon and Russel (2007)	√	√	√	√			√	√		√	√		√		
Chaikledkaew et al. 2009	√			√				√		√		√	√		
Zegeye et al. (2017)	√			√				√					√		

Health system constraints: A=Existing decision-making practices; B= Feasibility of resource use; C=Political and other stakeholder pressure
User characteristics: D=Lack of knowledge and understanding; E=Lack of awareness; F=Role of decision maker; G=Professional background or allegiance
Production and access to HTA methods: H=Lack of human capacity; I=Lack of needed data; J=Distrust in methods; K=Inability to generalise or transfer results from one setting to the other; L=Source of funding of studies; M=Inability to access studies; N=Irrelevance of studies to the needs of decision makers; O=Lack of involvement of decision makers in research
Note: Tick (√) means studies identified and reported the barrier.

Health system constraints

The majority of the barriers stated by decision makers are inherent to existing health system processes such as the decision-making process and/or feasibility of resource use.

Decision-making processes

For some decision makers, there were existing decision-making processes that did not allow for consideration of other methods. Some of the processes involved considering factors such as availability of resources, equity, benefits to the patient, burden of disease and political and stakeholder pressure. As stated by Zegeye and colleagues (120) even though some Ethiopian decision makers had knowledge of HTA methods, the nature and history of existing policies did not allow them to incorporate such evidence in their decision-making activities. Teerawattananon and Russell (6) came to a similar conclusion in relation to the Thailand health context.

Another characteristic of the decision-making process was the time needed for decision makers to make most of their decisions. For example, some senior managers and health administrators in Australia (122, 126) stated their inability to use HTA methods to inform their decisions was due to the urgency with which they needed to take those decisions compared to the time taken for researchers to conduct an evaluation. To mitigate this barrier, some respondents suggested researchers needed to have a greater understanding of processes involved in health decisions, and also the need to collaborate with decision makers in the conduct of their evaluations (6, 127-129).

Feasibility of resource use

The lack of autonomy in allocating resources was a major constraint indicated by decision makers who had a positive attitude towards HTA methods. This lack of autonomy results in their inability to shift resources from one program/intervention to the other. In the UK,

Australia, Thailand and Argentina, health administrators noted that their inability to reallocate resources within a fixed budget was a key restriction. Worthy of note is the fact that while those from developing countries considered budget constraint as inability to reallocate money for the conduct of such studies (6, 130), those in developed countries considered it as their inability reallocate resources to implement the results from HTA methods (31, 123, 124, 126, 129, 131).

It is usually assumed that decision makers would take advantage of HTA methods as these can inform disinvestment decisions where an intervention is deemed not to be cost effective, thus freeing up resources for other purposes in the long run. However, this tends not to be the case as most decision makers pursued other objectives such as equity and efficiency, not cost effectiveness. They also made short term decisions with expected immediate outcomes, which is contrary to HTA methods that use a longer time horizon in assessing the costs and benefits of an intervention. They also perceived that using findings from an HTA methods implied additional resources or forgoing an activity, instead of assisting them to make better choices, hence the importance of educating users on HTA methods and their relative utility compared to previous ways of making decisions.

Decision makers from developing country setting were of the view that institutionalising HTA and providing clear guidance for its use as well as making provisions for it in the health budget could improve its use. Arguably, this may not always be the case as some studies from countries where HTA was institutionalised reported otherwise. For example, in Australia, HTA methods are used to make reimbursement decisions by the PBAC and MSAC, which are all at the national level, hence its use at that level is widespread. However, very little use is reported at the hospital level (121, 126), where HTA methods are not used to inform the everyday decisions of health managers/administrators and clinicians such as purchasing medical devices or choosing a technique for a surgical procedure. A similar situation is observed in the UK

where use of HTA methods is limited at the local level among hospital managers and health authorities (31, 128, 131, 132).

User characteristics

All studies reported that lack of knowledge, awareness and understanding of HTA methods as major hindrances to their use by decision makers. However, peculiar to settings where its use was mandatory, was the fact that some decision makers were unaware of the existence of HTA methods, hence not using them (31, 121, 126, 131-133). To address this barrier, training of decision makers in HTA approaches through short courses or by incorporating it in their professional development programs was suggested.

While clinicians and pharmacists typically made decisions based on patient benefit rather than benefit to the population as a whole or cost to the health system, health administrators were concerned with being able to deliver services within the allocated budget, and policy makers with the costs and benefits to the institution and general population as a whole (6, 122-124, 127). Therefore, the use of HTA methods were not widespread among clinicians and pharmacists compared to health administrators and policy makers. Hence, an individual's professional background and role as elaborated earlier had an impact on what was deemed relevant for decision-making, and consequently the use of HTA methods. This also sheds light on the importance of a choosing an evaluation perspective that better suits the needs of a decision maker. For instance, a policy maker would prefer a health system or societal perspective rather than a patient perspective.

Conduct of and access to HTA methods

Conducting studies

Three barriers hindering the conduct of HTA methods were identified: unavailability of human and data capacity to conduct it, awareness and knowledge of the methodological approaches

underpinning its conduct, and a funding source. For all developing countries, a key challenge to the adoption of HTA methods was the lack of human resources to conduct such evaluations (5, 6, 119, 120, 130). Contrarily, in terms of conduct, most decision makers from settings where HTA methods were formalised (mostly developed countries) were deterred from using them because of their distrust in the methods. Decision makers from the UK stated that the use of assumptions in HTA introduce bias into findings, thus deterring them from using it (123, 124, 127-129, 131, 133). Those from Canada and Australia reported similar reservations (122, 125, 126). Possibly, these concerns may simply relate to lack of understanding of HTA methods, as the use of assumptions are inevitable since most studies cannot be entirely based on observational data, hence would require that some assumptions be made.

Other concerns with the methodological approach were the variations in methods and presentation of results, and the inability to generalise and transfer findings from one setting to another. The latter was particularly of great concern to decision makers from developing countries who had hoped that in the absence of the needed capacity to undertake HTAs, they could 'generalise' and use findings from other settings. In addition, some decision makers from the UK and Australia noted the lack of consideration of ethics and equity in HTA methods, such as economic evaluations, constrained their use (126, 132).

Again, because pharmaceutical companies are reliant on a positive finding from HTA methods for the reimbursement of their technologies, some decision makers from developed countries perceive any study sponsored by them as lacking credibility (123, 124, 129, 131, 132). However, even if these companies do not directly sponsor studies, the clinical efficacy estimates used in evaluations are recorded during clinical trials testing the technology, which are also sponsored by pharmaceutical companies. Hence, reporting better effectiveness will subsequently lead to better findings from evaluations, if same logic is to be followed.

Access to HTA products

Some decision makers suggested that the inability to access HTA findings hinders them from using them. Indeed, these were concerns of decision makers irrespective of the state of HTA institutionalisation at the time of data collection. For most decision makers in settings where the use of HTA methods was not formalised, their ability to access the results of HTA methods was a big barrier to using them (2, 5, 6, 119, 120, 130). On the other hand, for those in settings where HTA agencies existed, their ability to access HTA findings relevant to them in a timely manner was reported as a major influence on their use. For example, some decision makers from Australia (122, 126) and Canada (125) attributed the accessibility of HTA findings as a barrier to their use, as the information was usually unavailable at the time of decision-making. However, unlike day-to-day health decision-making, HTA methods require a longer timeframe for results to be available. Thus, relevant results from HTA methods might not be available for the day-to-day priority setting and procurement activities of decision makers.

In response to the barrier of producing and accessing products of HTA methods, decision makers suggested that the methods and presentation of results be standardised. They also felt that developing the capacity to conduct such studies and transferral of the available data to suit the local context was needed. Furthermore, the dissemination of such results and making them readily accessible to users in a simple format was suggested.

2.7 Limitations of the review

The review conducted on HTA practices included a range of 10 countries that satisfied the selection criteria. The criteria included income level of their population, the duration for which they have been using HTA as a technical tool to inform decision-making and the technical capacity. However, the thesis notes that, this might have introduced some bias in the

conclusions drawn about the differences in HTA practices in countries with different income levels.

Another limitation is the restriction of studies assessing the knowledge and perception of decision makers to only countries whose HTA agencies were reviewed (with the exception of those from developing countries). However, this was done to ensure consistency and coherence in the literature reviewed and also to define a scope as there is a larger body of literature in this subject area.

Lastly, the findings of this review are limited by the exclusion of the grey literature However, this grey literature was not included due to difficulty in accessing such data especially from developing countries.

2.8 Conclusion

This chapter has presented an overview of the literature on HTA, its use in selected countries and its utility and perceived barriers to its use. Relating the literature reviewed in this chapter to the Ghanaian context, the current challenges faced by the Ghanaian health system creates a conducive environment to explore the use of HTA methods to inform resource allocation decisions, most especially in reimbursement/funding under the NHIS. However, this thesis recommends that care be taken in the introduction of HTA methods for formal decision-making, as there is no direct association between its establishment and its actual use. Factors inherent in the health system, HTA methodology and user characteristics must be considered as these contribute to its use and non-use, and subsequently, intended benefits. The characteristics of the health systems described in studies conducted in developing countries that were anticipating the introduction of HTA for formal decision-making are similar to the Ghanaian health system. Therefore, it can be postulated that Ghanaian decision makers would have similar levels of knowledge of HTA methods, and share the same perceptions about the

barriers to its use, as decision makers in other developing countries. It is also expected that the knowledge and attitude of Ghanaian decision makers towards HTA would be similar to settings where HTA is not formally used or its diffusion was low, but different from settings where HTA is used formally and with better diffusion.

In addition, the conduct and use of HTA methods varies with each health system, hence it is not advisable to simply adopt a model from elsewhere for use. Rather, a country specific HTA process that is informed by relevant data must be pursued. There was also differences in the extent of, and willingness to use HTA methods observed among different types of decision makers. Therefore, in developing policies for the introduction or promotion of the use of HTA methods, it is imperative to consider the distinctive needs and decision-making practices of different types of decision makers in each context as one policy directive cannot address the needs of every decision maker.

3 HTA IN GHANA: PERCEPTION OF HEALTH WORKERS ABOUT THE DECISION-MAKING PROCESSES IN THE HEALTH SYSTEM

3.1 Introduction

This chapter presents results of research investigating the perception of clinical health workers about the decision-making process in the Ghanaian health system. As discussed in Chapter 2, the inadequate use of HTA methods has been attributed to factors including health system constraints such as pre-existing decision-making processes. The role of the decision maker has also been associated with the likelihood of him/her using HTA methods. For example, previous studies reported more use among health managers and national policy makers compared to clinical health workers in the same setting. Thus, the role of health workers who are decision makers at the clinical level, in ensuring that the intended benefits of HTA are achieved in the health system, cannot be overlooked.

It is evident that different types of decision makers make decisions within different contexts. Therefore, this chapter examines factors important for clinical decision makers in the Ghanaian health system. In Ghana, these type of decision makers do not make direct policy decisions. Rather, they implement decisions that are made by national, regional, district level decision makers and hospital administrators/managers. That is not to say they do not make any form of decisions in the health system. Their roles at the clinical setting also involve making decisions about patient care, which often includes choosing between alternative procedures and/or medicines and allocating some of the resources available, which are in turn affected by decisions made by policy makers.

Thus, it is appropriate to investigate health workers' perceptions regarding the current process of decision-making in the Ghanaian health system in addition to assessing factors relevant to

them for consideration in new health policies such as the introduction of HTA methods. The objectives of the research undertaken here were to assess:

1. the awareness of health workers about the current decision-making process in the health system;
2. the factors they perceive and what they recommend decision makers should consider;
3. who they believe should be part of the decision-making process;
4. their knowledge of and/or training in economic evaluation.

Primary data collected in a survey was used to address the above research questions. The next section presents the methods used in data collection and analysis. Section 3.3 presents the findings and these are interpreted and discussed in relation to the existing literature in Section 3.4. Section 3.5 concludes the chapter.

3.2 Methods

A cross-sectional survey was used. It provided an opportunity to explore the research questions using a large and representative sample to enhance the generalisability of the findings.

3.2.1 Study population

The study population consisted of health workers who make decisions at the clinical facility level. It included the main cadres of health workers in Ghana: medical doctors, physician assistants, nurses, anaesthetics and pharmacists. In addition to making clinical decisions, health workers are also seen as the users of policy directives and decisions, hence able to influence the adoption of policies, including the HTA findings.

3.2.2 Sampling frame

Health workers who worked in selected government owned facilities were sampled. These facilities were Komfo Anokye Teaching Hospital (KATH), Tema General Hospital, Ridge

Hospital, Achimota Hospital and Shai Osu Doku Hospital. The prospective sampling frame was derived from the Integrated Personnel and Payroll Database (IPPD) (IPPD – MOH, September, 2015) and the human resource database and gap analysis of the Ghana Health Service (HRD- GHS, 2015). Sampling was restricted to only those who worked in the government sector because there is data on the number and distribution of the different cadres of health workers in this sector. There is no data on the number and distribution of health workers in the private sector; this limits appropriate sample calculation and sampling. Therefore, government workers were deemed as an appropriate source of respondents recruited for the study.

Inclusion criteria

1. Health workers who worked in selected public (government owned) health facilities.
2. Anaesthetists include both nurse anaesthetists and anaesthesiologists who are mostly medical doctors.
3. Nurse managers who are defined in this context as ward in-charges at any particular shift and nurses in charge of a department (as seen in KATH). They are classified as senior nursing officers, principal nursing officers, senior nurse midwives, principal nurse midwives and deputy directors of nursing services.
4. Medical doctors including all physicians, surgeons and physician assistants at the facility.
5. Registered pharmacists who work at selected facilities and were present at the time of data collection.

Exclusion criteria

1. House officers (medical interns) who work at the KATH. It was assumed that these categories of medical doctors do not make direct decisions concerning patients since they work under the direct supervision of medical officers and specialists.
2. Health workers at privately owned facilities.
3. Staff nurses and nurse-assistants.
4. Non-medical and non-nursing staff such as paramedics, accountants and record keepers.

3.2.3 Sampling process and recruitment of study respondents

For representativeness of findings, a purposive sampling method was used. Health workers were sampled from health facilities deliberately chosen to include facilities that provide health care at the three tiers of the health system; primary, secondary and tertiary. This was necessary to ascertain the perception of health workers at both higher and lower levels of care as well as provide a representation of relatively well-resourced and poorly resourced health facilities, which is characteristic of the Ghanaian health system.

Health facilities at the primary and secondary level of care were selected randomly while the tertiary hospital were conveniently selected due to access. Health facilities included in the study were KATH, the second largest of four tertiary hospitals in Ghana; two secondary level hospitals, Ridge Hospital and Tema General Hospital; and two other primary hospitals, Achimota hospital and Shai Osu Doku District Hospital.

A list of all health facilities that delivered services at the different levels of care within the study area was obtained from official government websites. Facilities under each level of care were randomly selected using a paper ballot with the exception of tertiary level of care facility which was purposively selected based on accessibility and approval from the hospital. KATH, the second largest tertiary hospital, two secondary level hospitals (Ridge Hospital and Tema

General Hospital) and two other primary hospitals; Achimota hospital (medium size) and Shai Osu Doku District Hospital (small size) were selected.

Given the inclusion criteria of the survey, eligible respondents (that is, the number of health workers such as nurses and doctors by their employment status) were obtained from the Integrated Personnel and Payroll Database (IPPD) (IPPD – MOH, September, 2015) and the human resource database and gap analysis of the Ghana Health Service (HRD- GHS, 2015). It was assumed that these databases capture the total number of health workers who are employed by the government, hence a good enumeration of study population. The Yamane (1995) simplified formula for sample size estimation was used to estimate the required sample size to be 305 at the 0.05 criterion level. A non-response rate of 15% was assumed, hence allowance was made for that by adding the proportion (45 = 15% 0f 305) to the estimated sample size. In all 350 participants were sampled.

Recruitment of respondents from health facilities was done based on the proportion of health personnel in each facility. At the facility level too, respondents were drawn from each cadre of health personnel using the proportion each constituted in the entire health personnel population at the facility. This approach was used to minimise under-representation or over-representation of a particular facility and group of study respondents. The distribution of respondents recruited from each health facility is presented in Table 3-1.

Table 3-1: Type and number of health workers and sample allocation

Facility	Doctors	Pharmacists	Anaesthetists	Nurse managers	Total
KATH	36	15	9	90	150
Tema General Hospital	23	7	5	55	90
Ridge Hospital	17	5	3	35	60
Achimota Hospital	10	3	2	10	25
Shai Osu Doku District Hospital	7	1	1	15	25
Total	**93**	**31**	**20**	**205**	**350**

Abbreviation: KATH: Komfo Anokye Teaching Hospital.

In total, 350 respondents were invited to participate in the survey. The survey period lasted for three months: March to May 2016.

3.2.4 Data collection technique and instrument

A written information sheet and a consent form were given to respondents to sign regarding their voluntary participation (Appendix 2, Document 1). Questionnaires were delivered face-to-face to respondents at their work places for self-completion (See Appendix 2, Document 2 for the full questionnaire). Respondents were given three face-to-face reminders to complete the questionnaire: the first at the end of the day the questionnaire was delivered; the second, a week after delivery and the third a month after delivery. The questionnaire included eight main sub-sections:

1. Background to the study which explained the study's purpose and terminologies used. The background also had information on the definition and forms/types of decision-making respondents were to consider. This included allocation of resources and selection of health services and medicines under the NHIS.
2. Demographics of respondents.
3. Awareness of health decision-making process in the Ghana health system.
4. Factors perceived as considered by decision makers for decision-making.
5. Factors recommended for consideration in decision-making.
6. Categories of health workers perceived to be involved in decision-making.
7. Categories of health workers recommended to be involved in decision-making.
8. Knowledge of and/or training in economic evaluation.

A 5-point Likert scale was used to assess the awareness of health personnel of the decision making process in the Ghanaian health system. For objectives 4-7, the thesis used a ranking method, an approach utilised in a previous study that assessed the perception of decision

makers on health technology decisions and priority setting at the institutional level in Australia (134). Limitations of the ranking approach include 'order bias' where respondents may rank the first set of items positively. In ranking, the researcher is unable to identify why an item is important or unimportant to the respondents. In addition, the ranking approach is limited by the lack of cardinality; that is items are ranked in order but the score attached does not indicate the distance between them. Meanwhile, there may be instances that respondents may view items as equal. Therefore, respondents may have been forced to choose between two or more items they may have wished to rank equally. These limitations were addressed as much as possible in the rest of the chapter (see section 3.4.1). Each questionnaire took approximately 15-20 minutes to complete. The majority of respondents (60%) completed the questionnaire within a week after they were delivered.

The questionnaire was pre-tested in a pilot study to enhance its quality. The pilot study was conducted at the Holy Family Catholic Hospital in the Central region, after permission was sought from the hospital management. Respondents surveyed included all categories of health workers as defined in the inclusion criteria. The results of the pilot study were not included in the main study because the data collection tool was revised. The wording of the ranking questions was changed after the pilot study to ensure the correct responses are elicited and to reduce non-response rates for those questions due to lack of understanding of the questions. For instance, respondents did not understand 'ranking' as apportioning one number per variable in a hierarchical manner, hence assigned the same numeric value to more than one variable. Therefore, the question was reworded by adding number in brackets next to the word rank, followed by the ranking order as shown below:

Initial question: Please **rank** the following in order of importance the factors **(in your opinion)** that influence decision makers in the current decision-making process in the Ghana health system. **1= most important and 10 = least important**

Final question after pilot**:** Please **rank (number)** the following from 1 to 10 (**1= most important and 10 = least important)** in order of importance the factors **(in your opinion)** that influence decision makers in the current decision-making process in the Ghana health system.

(Note: For the purposes of analysis and presentation of results, variables were recoded such that 1= least important and 10 = most important).

3.2.5 Data analysis

The data were entered and stored in IBM Statistical Package for the Social Sciences (SPSS) software version 23. Data analysis was conducted using IBM SPSS software version 23 and Microsoft Excel 2017. Descriptive statistics were used for the demographic data provided by survey respondents and their answers to the questions in the survey. The 5-point Likert scale responses were converted to 3-point scale: disagree (consisting strongly disagree and disagree), uncertain, and agree (comprising agree and strongly agree) for further analysis.

It was hypothesised that respondents' awareness of the Ghanaian health system decision-making process and knowledge of and/or training in economic evaluation would be dependent on their characteristics such as primary discipline, current role and years of working experience. Thus to test this hypothesis a Chi-square test of association was conducted to examine the relationship between the characteristics of respondents and study variables: the awareness of the decision-making process and the knowledge of and/or training in economic evaluation. This test was chosen for the study because responses of the independent variables were categorical (disagree, uncertain and agree) and had a single outcome (awareness of decision-making and knowledge of and/or training in economic evaluation) (135).

For the ranking questions, the relative importance of each variable was assessed by estimating the relative importance index of each variable using the formula (136):

$$Relative\ importance\ index\ (RII)\ = \frac{\sum W}{A \times N}$$ Equation 1

Where W is the weighting given to each factor by respondents,

A is the highest weight (which is 10 in this case),

N is the total number of respondents.

The relative importance index ranges from 0 to 1. The smaller the relative importance index estimated for a variable, the lower the relative importance attached to that variable by the respondents and vice versa. This was done to ascertain the value respondents placed on each variable for structuring the decision-making process: recommendations on factors to consider when making decisions in the Ghana health system, and which health stakeholders should be involved (have the most influence) on decision-making. The differences between relative importance attached to each variable (decision-making factor and stakeholders) by the different categories of health workers were also assessed.

3.3 Results

Three hundred and six (n=306) out of a possible 350 respondents completed the survey. Therefore, a response rate of 87% was achieved. Of the non-responders, 16 were in the 'others' category (n=31) (including those whose primary disciplines were not captured in the questionnaire), 13 were nurses (n=160), ten were medical (n=86), and five were pharmacists (n=29).

3.3.1 Characteristics of study respondents

Table 3-2 presents the characteristics of survey respondents. Forty-four percent (n=136) of clinical health decision makers who answered the questionnaire were from KATH whereas Achimota Hospital was the health facility with the fewest respondents (n=15). The distribution

of respondents in health facilities in this survey is representative of the allocation of health workers at the different levels of care of the Ghanaian health system.

The majority (65%) of the respondents were female. About 62% of respondents reported having a bachelor's degree. For analysis, the category 'others' under the primary discipline includes administration, management, public health and other training not captured in the questionnaire. The category Medical under the current position consists of Physicians, Surgeons and Physician Assistants whereas 'Others' includes health workers who were also researchers (in addition to their clinical roles), and anaesthetists. Nurses comprised of the majority (52%) of respondents followed by Medical (28%) and Pharmacist (10%), which reflects the distribution of the health workforce in Ghana. Fourteen percent (14%) of respondents had been working in the health sector for more than ten years, whereas 50% had been working between one and five years.

Table 3-2: Characteristics of Study Respondents

Characteristics of study respondents	Frequency (%)
Name of facility (n=306)	
Komfo Anokye Teaching Hospital	136 (44)
Tema General Hospital	77 (25)
Ridge Hospital	55 (18)
Achimota Hospital	15 (5)
Shai Osu Doku Hospital	23 (8)
Sex (n=306)	
Male	106 (35)
Female	200 (65)
Highest level of education (n=303)	
Diploma	60 (20)
Advanced Diploma	22 (7)
Bachelor degree	188 (62)
Masters' degree	30 (10)
Ph.D	3 (1)
Primary discipline (n=304)	
Medicine	93 (31)
Pharmacy	30 (10)
Nursing	166 (54)
Others	15 (5)
Current position (n=306)	

Characteristics of study respondents	Frequency (%)
Medical	86 (28)
Pharmacist	29 (10)
Nurse	160 (52)
Others	31 (10)
Years of work experience (n=304)	
Less than one year	43 (14)
1 to 5 years	153 (50)
6 to 10 years	67 (22)
More than ten years	41 (14)

3.3.2 Perception of study respondents on the current process of decision-making in the Ghanaian health system

Table 3-3 presents the perception of health workers about the current decision-making processes when the 5-point Likert scale ratings were categorised into three main ratings: agree (strongly agree and agree), uncertain and disagree (strongly disagree and disagree). (Appendix 3, Figure 11-3).

While 45% of respondents disagreed with the statement: "I am aware of the current process of making decisions in the Ghana health system", 37% agreed with the same statement. The remainder of the respondents were uncertain. In most of the categories, respondents either agreed or disagreed with the statements describing the characteristics of the health decision-making process.

The majority of respondents also felt that their opinions did not matter when it came to making decisions in the health system (64%), which was also the case for their perception of the importance of the input of every Ghanaian in health decisions (67%). While 59% of respondents perceived the decision-making process as unfair, 17% perceived otherwise. The remainder were not certain whether it was fair or not. In terms of using evidence to make health decisions, 42% of respondents perceived decision makers did not make decisions based on the appropriate evidence. It is worth noting that the questionnaire did not explain what evidence-based decision-making was, hence it is unclear how respondents interpreted this statement.

Table 3-3: 3-point Likert scale ratings of the perception of clinical decision makers about the current process of decision-making in the Ghanaian health system

	Disagree n (%)	Uncertain n (%)	Agree n (%)
I am aware of the current process of decision-making in the Ghana health system (n=302)	136 (45)	55 (18)	111 (37)
All the relevant stakeholders are involved in the current process of decision-making in Ghana (n=305)	133 (44)	78 (25)	94 (31)
The current process of decision-making in the Ghana health system is all inclusive (n=304)	156 (51)	81 (27)	67 (22)
The current process of decision-making in the Ghana health system is appropriate (n=299)	156 (52)	83 (28)	60 (20)
The current process of decision-making in the Ghana health system is fair (n=302)	179 (59)	73 (24)	50 (17)
The current process of decision-making in the Ghana health system is transparent (n=298)	182 (61)	67 (23)	49 (16)
My opinion is influential in the current process of decision-making in the Ghana health system (n=303)	195 (64)	43 (14)	65 (22)
The current process of decision-making in the Ghana health system is evidence-based (n=304)	126 (42)	95 (31)	83 (27)
The current process of decision-making in the Ghana health system ensures the appropriate use of public money (n= 304)	158 (52)	85 (28)	61 (20)
The current process of decision-making in the Ghana health system ensures that every Ghanaian can make an input in the decisions (n=305)	205 (67)	56 (19)	44 (14)

The 5-point Likert scale was collapsed into 3: strongly disagree and disagree, uncertain, and disagree and strongly disagree for easy description in this table.

3.3.3 The association between respondents' awareness of the current process of making decisions in the Ghanaian health system and other study variables

To test for the strength of association between the variables, the ratings of the ten items were categorised into disagree (strongly disagree/disagree), uncertain and agree (agree/strongly agree). Table 3-4 presents the test of association between some of the characteristics of respondents and their perceived awareness of the current decision-making process in the Ghanaian health system. There was a statistically significant association between primary discipline ($p < 0.01$), current position/role ($p < 0.01$) and level of care ($p < 0.01$), and their perceived awareness of the decision-making process. The respondents' highest level of education and years of working experience in the health system were not significantly

associated with their perceived awareness of the current process of making decisions in the Ghanaian health system.

Table 3-4: Association between respondents' perceived awareness of the current process of decision-making in the Ghanaian health system and their characteristics

	I am aware of the current process of decision-making in the Ghana health system					
	Disagree		Uncertain		Agree	
	n	%	n	%	n	%
Highest level of education						
Diploma	33	55	6	10	21	35
Advance diploma	10	48	2	10	9	43
Bachelor degree	83	44	37	20	67	36
Masters' degree	9	32	10	36	9	32
Ph.D	0	0	0	0	3	100
$X^2(10)=17.46$ p-value=0.07; Phi and Cramer's V=0.24, p-value=0.07						
Years of work experience in the health system						
Less than one year	16	37	12	28	15	35
1 to 5 years	70	46	28	18	54	36
6 to 10 years	33	50	7	11	26	39
More than ten years	16	41	8	21	15	38
$X^2(8)=6.28$, p-value=0.62; Phi and Cramer's V=0.14, p-value=0.62						
Primary discipline*						
Medicine	34	37	15	16	43	47
Pharmacy	5	17	12	40	13	43
Nursing	89	55	25	15	49	30
Others	7	47	3	20	5	33
$X^2(6)=23.63$, p-value=0.00; Phi and Cramer's V=0.28, p-value=0.00						
Current position/role*						
Medical	32	38	14	16	39	46
Pharmacist	5	17	12	41	12	41
Nurse	91	58	24	15	43	27
Others	8	27	5	17	17	57
$X^2(6)=32.55$, p-value=0.00; Phi and Cramer's V=0.33, p-value=0.00						
Level of care*						
Primary care	10	29	7	20	18	51
Secondary care	48	37	24	18	59	45
Tertiary care	78	57	24	18	34	25
$X^2(4)=18.43$ p-value=0.00; Phi and Cramer's V=0.25, p-value=0.00						

*The characteristic of a respondent is statistically associated with their awareness of the current process of decision-making in the Ghana health system

3.3.4 Factors (perceived and recommended) taken into consideration in the current process of decision-making in the Ghana health system

On the scale of 1 to 10 where 1 represents the least important and 10 the most important, respondents ranked what they perceived decision/policy makers considered as important when

making decisions in the Ghanaian health system. Table 3-5 presents the relative importance index values for each variable and their corresponding overall rankings. Overall, disease burden was judged as the factor considered as most important while equity was judged least important by decision makers, although it is interesting to note that diseases of the poor is ranked highly.

Table 3-5: The relative importance index and rankings of factors (perceived and recommended) for decision-making

Factors considered for decision-making	Relative importance index		Rank	
	Perceived	Recommended	Perceived	Recommended
Disease burden (severity of disease	0.64	0.73	10	10
Population group to benefit	0.62	0.64	9	9
Diseases of the poor	0.60	0.61	8	8
Geographical area	0.59	0.59	7	7
Cost of the equipment, drug, treatment	0.58	0.49	6	3
Evidence of safety of the equipment, drug, treatment	0.55	0.54	5	4
Impact on budget	0.53	0.36	4	1
Evidence of effectiveness of equipment, drug, treatment	0.51	0.56*	3	6*
Evidence of cost effectiveness (i.e. the cost per quality life year gained)	0.47	0.46	2	2
Equity	0.37	0.56*	1	5*

NB: the higher the relative importance value, the higher the relative importance attached to the variable, hence the higher the ranking and vice versa (where 1 is equivalent to least important and 10 as the most important factor). *The rankings of the variables with the same value was arrived at by looking at the value for more than two decimal places (not presented in this table).

When asked to recommend factors that decision makers should consider, respondents suggested disease burden as the most important and impact on the overall budget the least important. Disease burden, population group to benefit, diseases of the poor, geographical area and evidence of cost effectiveness were all ranked at the same level/point for both perceived and recommended factors. Figure 3-1 presents the relative importance attached to what was perceived and what was recommended as factors to be considered by decision makers for health decision-making.

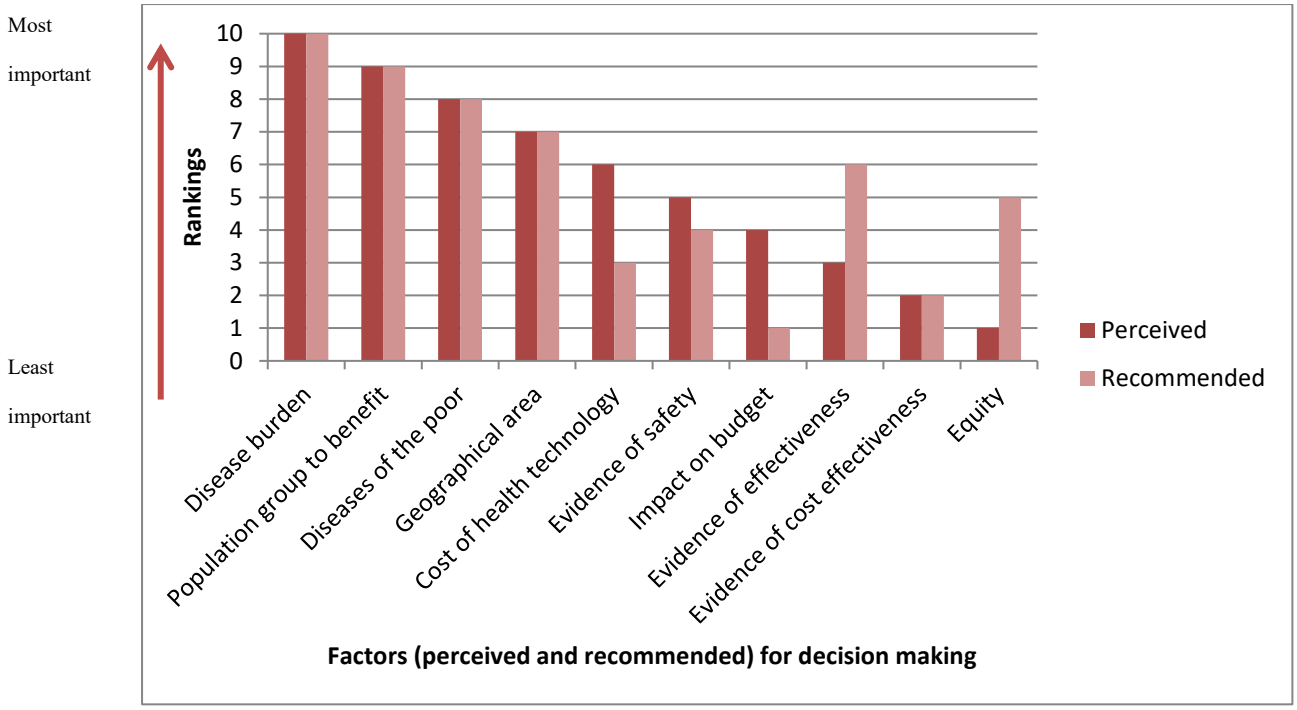


Figure 3-1: Perceived and recommended factors for consideration in decision-making of the Ghanaian health system

When responses were stratified according to the current position/role of respondents, there were some differences and similarities in what were perceived to be factors used by decision makers and what were recommended as factors to be considered in decision-making. The factors perceived by the different categories of health workers as currently considered by decision makers in the Ghanaian health system are presented in Figure 3-2. Except for factors 'disease burden' and 'population group to benefit' that were perceived as the most important factors currently considered by decision makers by all respondents, there were notable differences in the rankings of the remaining factors. For instance, all health workers ranked the factor 'impact on budget' differently. While medical personnel perceived that this was currently the 6th most important factor, other personnel perceived it to be the least important. In addition, while medical, nurses and pharmacists perceived 'equity' to be the least important factor currently considered by decision makers, other health workers perceived it to be the 5th most important factor.

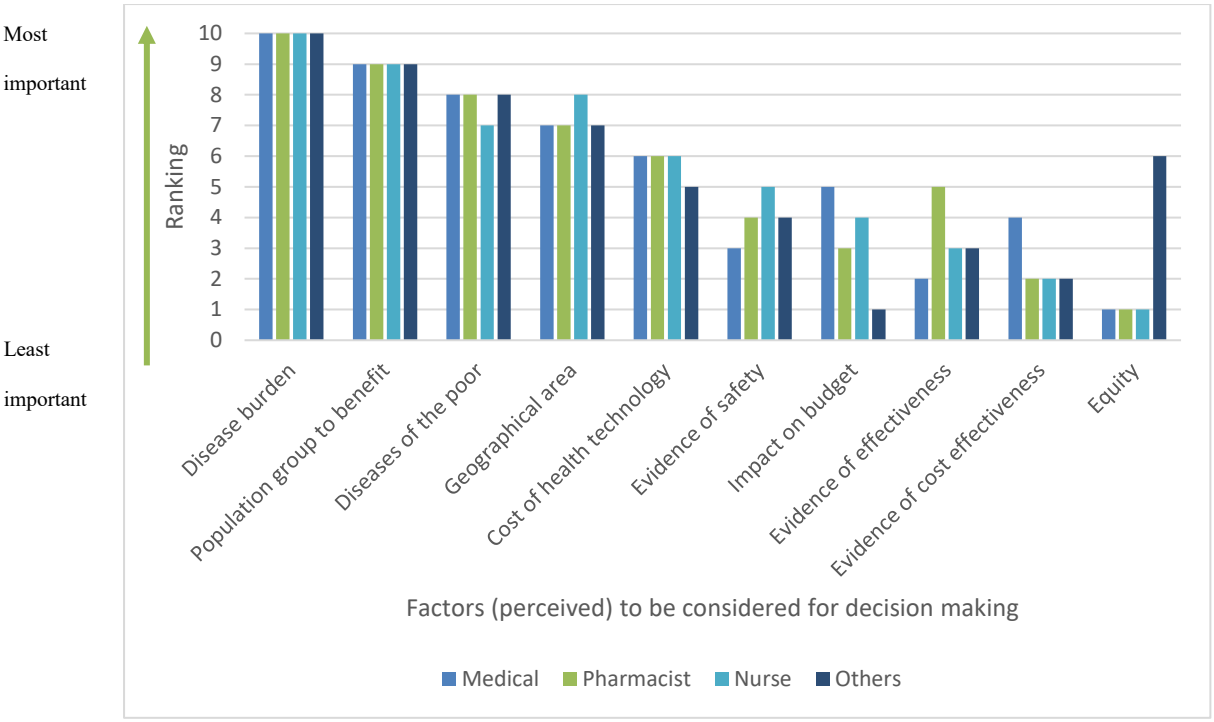


Figure 3-2: Perceived factors used for decision-making stratified by the different categories of health workers

In addition, Figure 3-3 presents some differences in the perception of respondents at the different levels of care. There were variations in the rankings of all factors except 'disease burden' for all levels, 'geographical area' for tertiary and primary, 'cost of health technology' for secondary and tertiary, and 'evidence of cost effectiveness' and 'impact on budget' for primary and secondary levels.

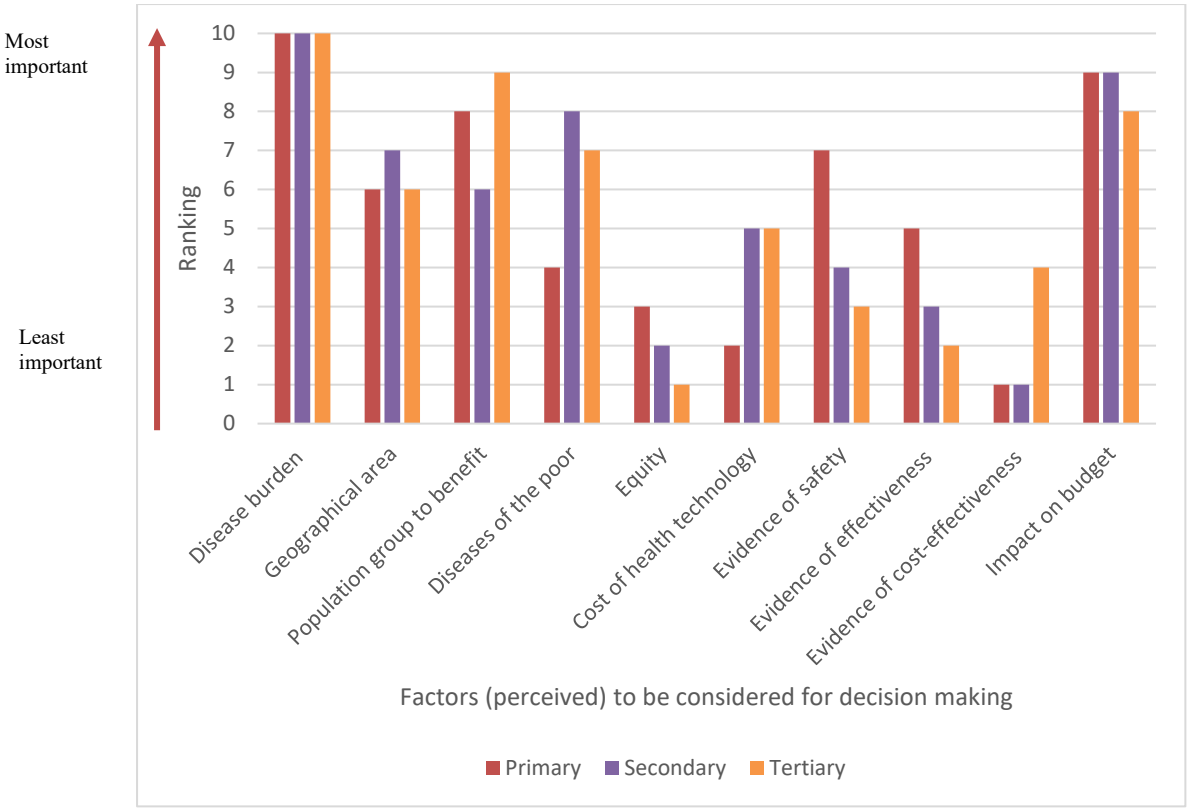


Figure 3-3: Perceived factors used for decision-making stratified by the levels of care respondents' work in the health system

Figure 3-4 presents the factors recommended by respondents with different roles in the health system as important, therefore be considered by decision makers in their decision-making processes. Factors 'disease burden', 'impact on budget' and 'evidence of cost effectiveness' were accorded the same importance by the different categories of health workers: most important, least important and the second least important respectively. Conversely, the other factors were given different emphases. For example, while medical personnel recommended that 'equity' be considered as the 7th most important factor, nurses ranked it as 4th and other personnel as 2nd most important. Medical and nursing personnel recommended the factor 'population group' to be the 2nd most important factor to consider for making health decisions. Pharmacist recommended 'diseases of the poor' as 2nd most important factor and evidence of safety and effectiveness of the health technology as the 3rd and 4th most important factor for decision-making respectively. Nurses also regarded 'disease of the poor' and 'evidence of

effectiveness' of the health technology as 3rd and 4th most important factors. Lastly, medical personnel recommended that factor 'geographical area' and 'disease of the poor' as the 3rd and 4th factor respectively.

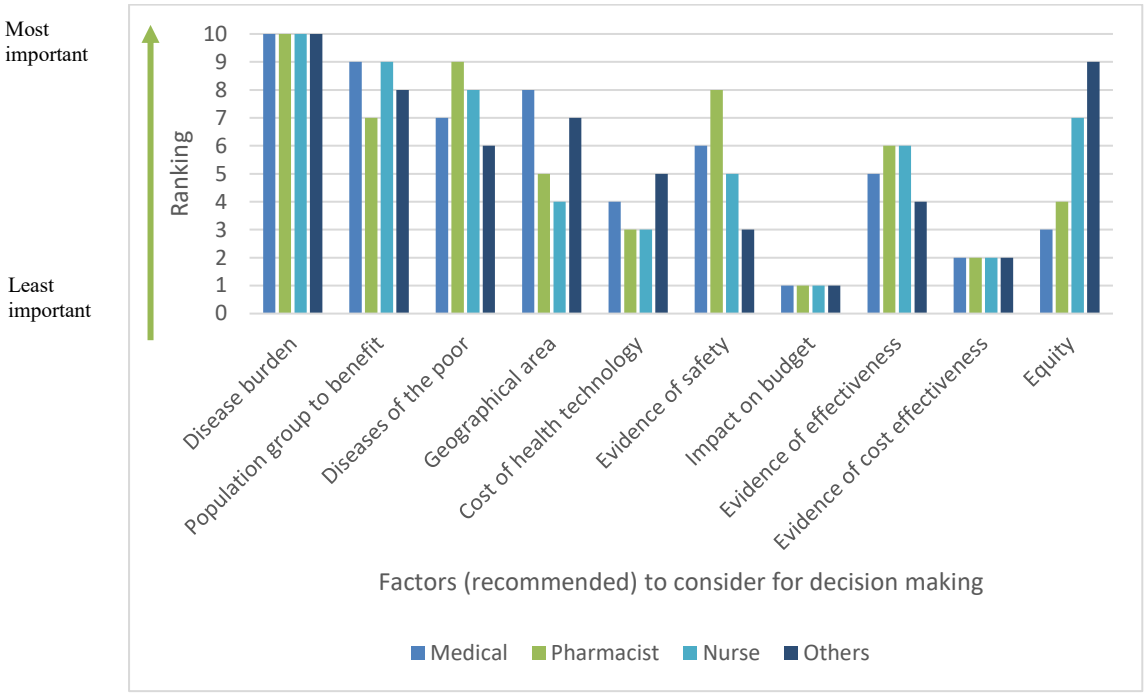


Figure 3-4: Factors recommended for decision-making stratified by the different categories of health workers

Likewise, there were some differences in the factors recommended by respondents at the primary, secondary and tertiary levels: 'disease of the poor' and 'evidence on safety' of the health technology. 'Disease burden' was ranked the most important decision-making factor by all respondents irrespective of the level of care they worked in (Figure 3-5). They also accorded 'impact on budget' and 'evidence of cost effectiveness' the same level of importance: least important and second least important respectively. While, primary and secondary level of care workers thought 'equity' should be the fifth most important factor to consider, tertiary level workers chose it as the third most important factor.

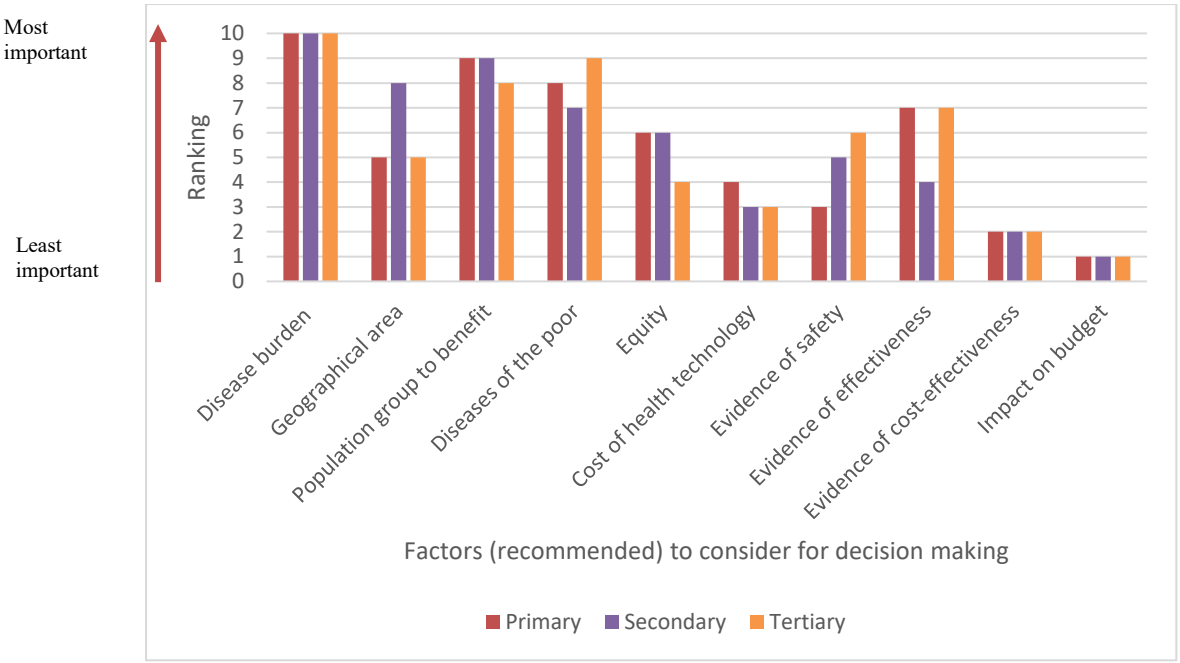


Figure 3-5: Factors recommended for decision-making stratified by level of care respondents work in the health system

3.3.5 Influential stakeholders (perceived and recommended) in the decision-making process of the Ghanaian health system

On a scale of 1 to 10 where 1 is the least influential and 10 the most influential, respondents ranked the stakeholders they perceived as influencing decisions made in the Ghanaian health system. Table 3-6 presents the results of the relative importance index and their corresponding rankings derived from the questionnaires. Overall, politicians were seen to have the most influence while consumers/patient groups were thought to have the least influence. Respondents recommended that physicians should have the most influence, followed by health managers, and expert groups. On the other hand, they suggested politicians as stakeholders should have the least influence on the decision-making process in the Ghanaian health system, followed by health economists. Figure 3-6 demonstrates the rankings of stakeholders as perceived and recommended by respondents to be involved in decision-making in the health system.

Table 3-6: The relative importance index and rankings of stakeholders perceived and recommended to have influence in decision-making in the Ghanaian health system.

Stakeholders to have influence in decision-making	Relative importance index		Ranks	
	Perceived	Recommended	Perceived	Recommended
Politicians	0.76	0.41	10	1
Heads of institutions	0.65	0.55	9	5
Health managers/administrators	0.63	0.62*	8	9*
Expert groups	0.62	0.62*	7	8*
Physicians	0.58	0.77	6	10
Health economists	0.48	0.43	5	2
Academics/researchers	0.46	0.48	4	4
Pharmacists	0.44	0.56	3	6
Nurses	0.44	0.59	2	7
Consumer/patient groups	0.43	0.46	1	3

Note: The higher the relative importance index, the higher the relative importance attached to the variable, hence the higher the ranking (where 1 is equivalent to least influential and 10 to most influential stakeholder)
*The rankings of the variables with the same value was arrived at by looking at the value for more than two decimal places (not presented in this table).

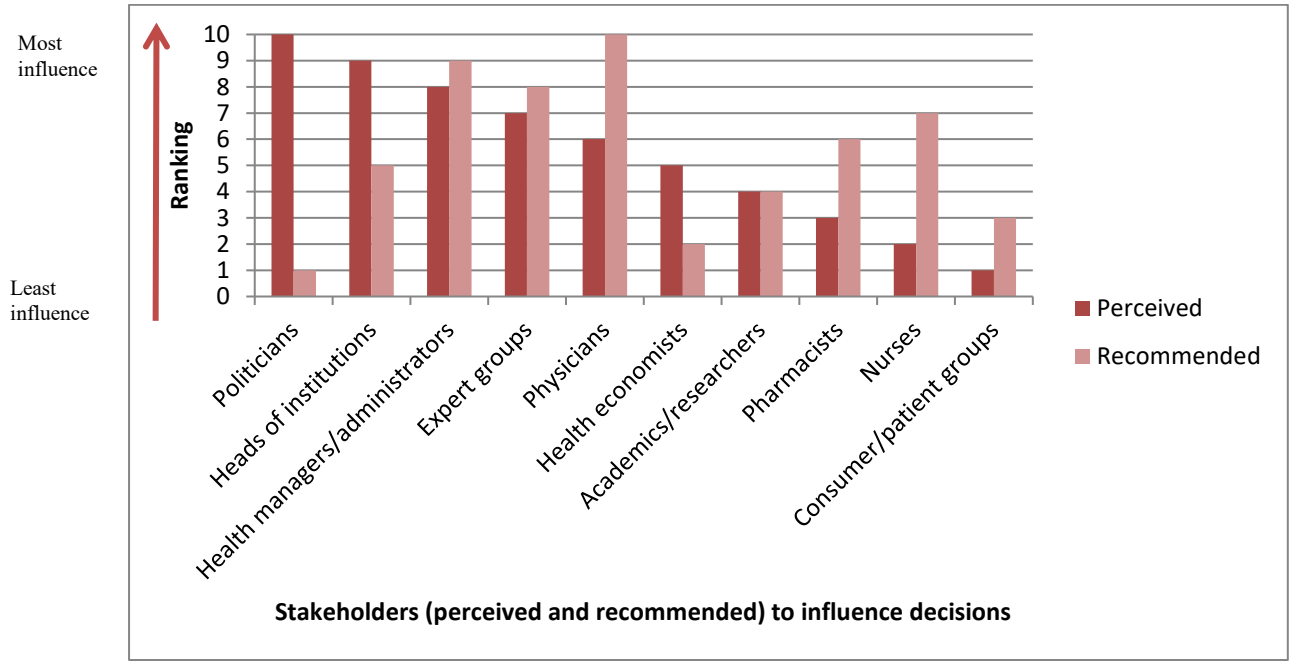


Figure 3-6: Stakeholders (perceived and recommended) influencing the current decision-making process in the Ghana health system

However, when stratified by category of health worker (current role/position), there were marked differences in respondents' perceptions about which stakeholders had influence in the decision-making process. Figure 3-7 presents these results. For example, while pharmacists'

perceived physicians as stakeholders with the most influence, medical personnel perceived politicians as most influential, and nurses and other health personnel perceived heads of government institutions as most influential. Another instance worth mentioning is the fact that all health personnel including nurses perceived nurses as either the 2nd or 3rd stakeholder with the least influence in the decision-making process. Also, while nurses and other health personnel agreed on the influence of six stakeholders, nurses and pharmacists only agreed on three.

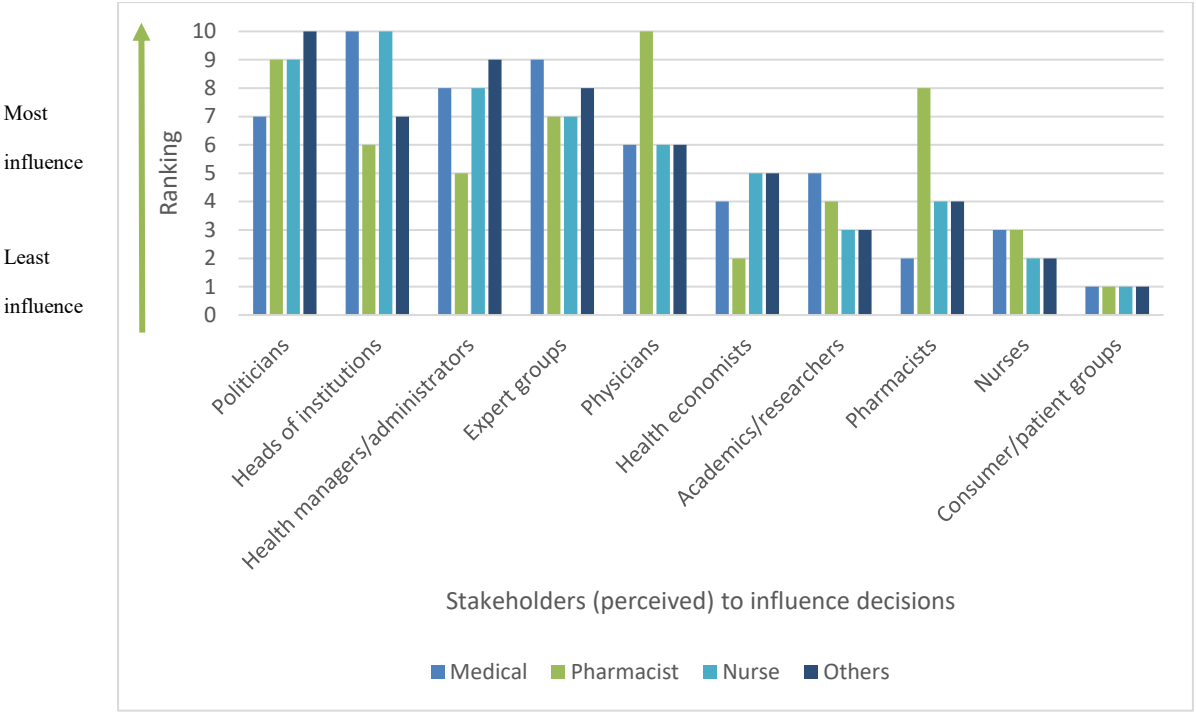


Figure 3-7: Differences in the perception of different categories of health workers for stakeholders with influence on the decision-making process

Similarly, when stratified by the level of care respondents' positioning in the health system, there were some differences in perceptions about the influence of various stakeholders on the decision-making process (Figure 3-8). For instance, while primary level workers thought politicians had the most influence, secondary and tertiary level workers perceived heads of institutions and health managers/administrators as most influential respectively. All health workers perceived consumers/patient groups were the stakeholders with the least influence.

Primary and secondary level workers agreed on the degree of influence of expert groups and pharmacists.

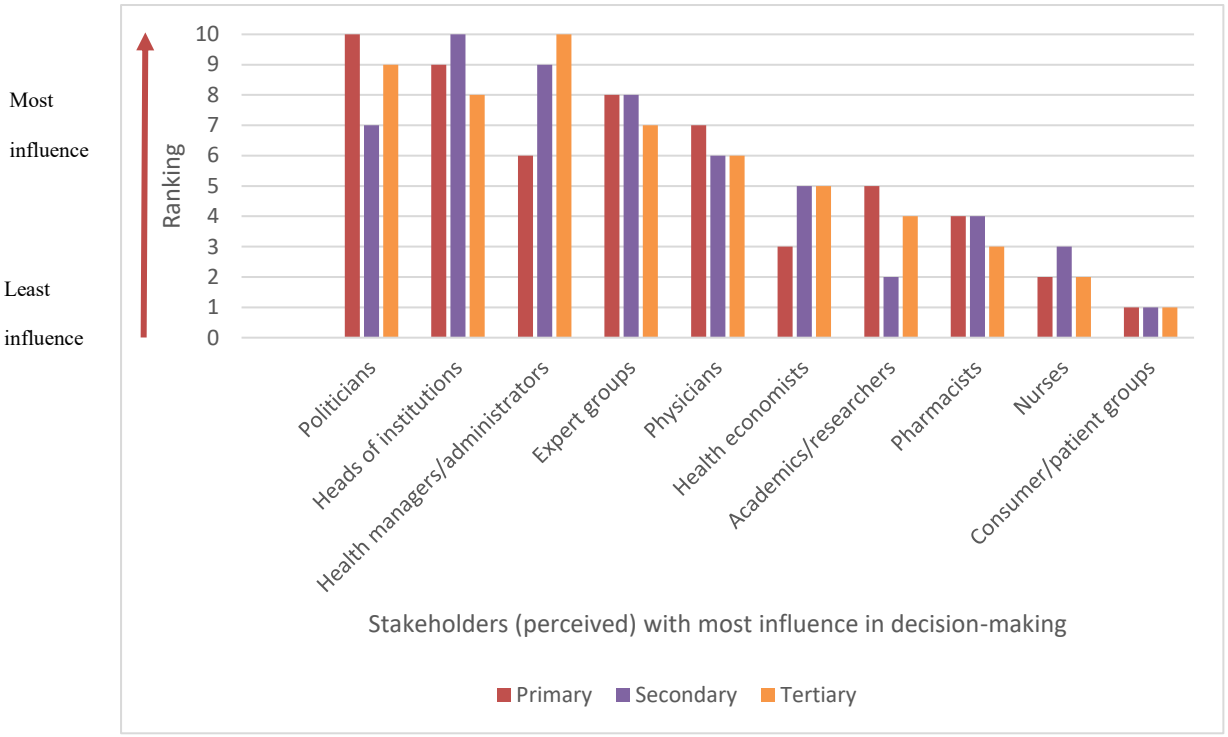


Figure 3-8: Perception of health workers at different levels of care about stakeholders with influence on the decision-making process

Figure 3-9 presents which stakeholders the different categories of health workers recommended should influence health decision-making in Ghana. All categories of health workers recommended 'politicians' should have the least influence. There were however differences in the recommendations of the relative importance of the remaining stakeholders in influencing health decision-making. Medical and other health personnel recommended that physicians have the highest influence. Pharmacists and nurses on the other hand suggested 'expert groups' and 'health managers'. There was a sharp difference between pharmacists and medical personnel compared to nurses and other health personnel when it came to what role 'academics/researchers' should play in health decision-making. While pharmacists and

medical personnel recommended them to be the 4th most influential stakeholders, nurses recommended them as 2nd least and other health personnel also suggested them to be the 3rd least most influential stakeholder. Consumers were recommended to be the 4th, 3rd and 2nd least influential stakeholders by nurses, pharmacists and medical personnel respectively.

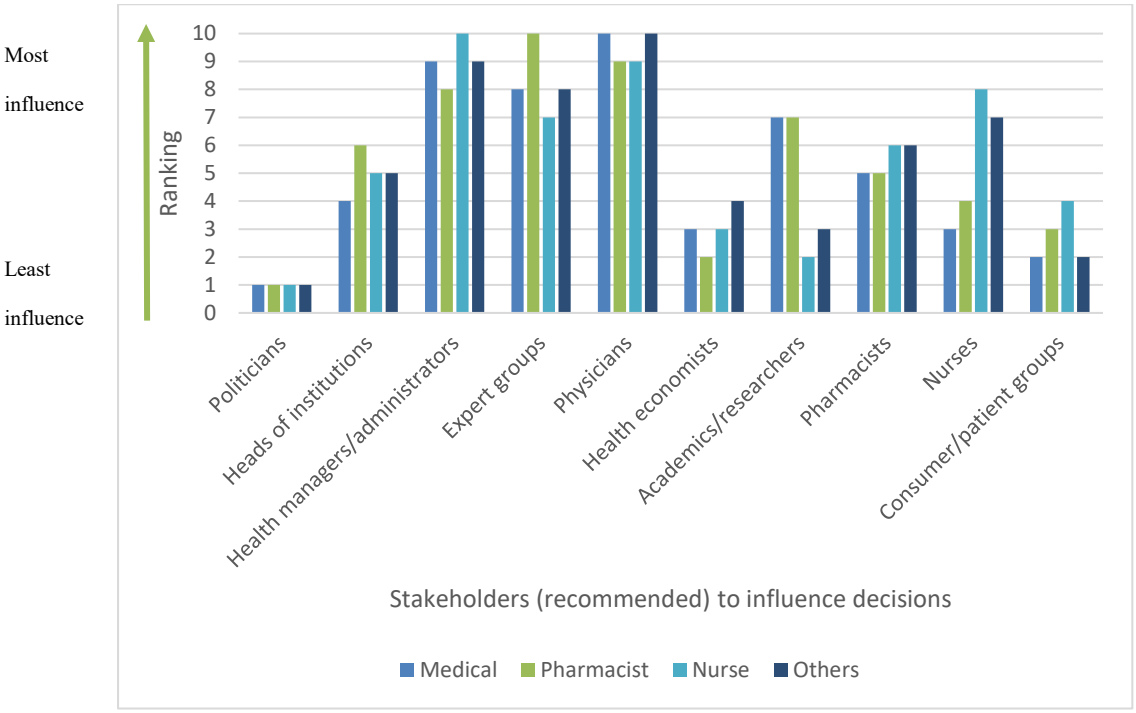


Figure 3-9: Differences in the recommendations of different categories of health workers for stakeholders to have influence on the decision-making process

Likewise, there were differences in the opinions of health workers at the different levels of care concerning which stakeholder they thought should have the most influence in decision-making, with the exception of politicians who were recommended to have the least influence (Figure 3-10). Nurses, physicians and health managers were recommended to be the stakeholders with the most influence in decision-making, by primary, secondary and tertiary level of care workers respectively. In addition, 'academics/researchers' were ranked differently by each category of respondent. There was a sharp difference between the level of influence consumers/patient groups were recommended to have on decision-making by health workers at the primary level compared to those at the tertiary and secondary levels. While the former proposed this type of

stakeholder as the third most influential, the secondary and tertiary level workers recommended them as the second least influential.

Figure 3-10: Differences in the recommendations of respondents working at different levels of care for stakeholders to have influence on the decision-making process

3.3.6 Knowledge of and/or training in economic evaluation

Figure 3-11 presents the proportions of clinical health workers with knowledge of and/or training in economic evaluation. Of the 296 respondents who answered this question, 242 (82%), reported having no knowledge and/or training, while the remaining 54 (18%) said they had knowledge and/or training in economic evaluation.

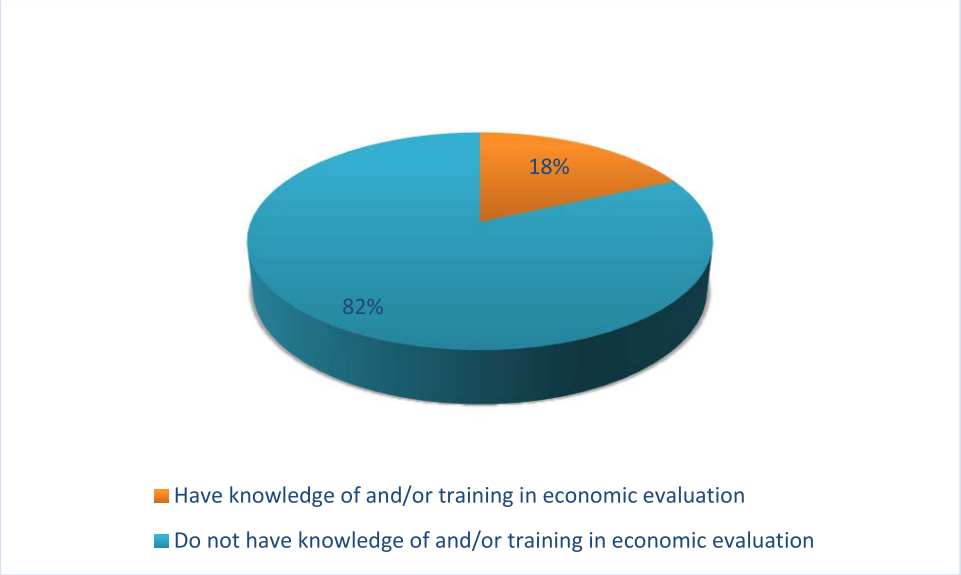


Figure 3-11: Respondents knowledge of and/or training in economic evaluation

The results in Table 3-7 showed a statistically significant association between respondents' knowledge of and/or training in economic evaluation and the characteristics of highest level of education, primary discipline and current position/role in the Ghanaian health system. However, respondents' knowledge of and/or training in economic evaluation were not statistically significantly associated with their years of working experience or the level of care they were working in (Table 3-7).

Table 3-7: Association between knowledge or training in economic evaluation and primary discipline and current position of respondents

	Knowledge or training in economic evaluation			
	Yes		No	
	n	%	n	%
Highest level of education*				
Diploma	11	20	44	80
Advanced diploma	4	18	18	82
Bachelor degree	27	15	157	85
Masters' degree	10	35	19	65
Ph.D	2	67	1	33
Missing value	0	0	3	100
X(5) = 12.20, p=0.03; Phi and Cramer's V = 0.20, p = 0.03				
Years of working experience in the health system				
Less than one year	9	21	33	79
1 to 5 years	27	19	119	81
6 to 10 years	11	17	54	83
More than ten years	7	17	34	83
Missing value	0	0	2	100
X(4) = 0.85, p=0.93; Phi and Cramer's V = 0.05, p = 0.93				
Primary discipline*				
Medicine	24	27	65	73
Pharmacy	4	13	26	87
Nursing	22	14	139	86
Others	4	29	10	71
X(3) = 8.24, p=0.04; Phi and Cramer's V = 0.17, p = 0.04				
Current position*				
Medical	24	29	58	71
Pharmacist	3	10	26	90
Nurse	20	13	134	87
Others	7	23	24	77
X(3) = 11.14, p=0.01; Phi and Cramer's V = 0.19, p = 0.01				
Level of care				
Primary	9	17	27	11
Secondary	22	41	102	42
Tertiary	23	42	113	47
X(2) = 1.28, p=0.53; Phi and Cramer's V = 0.07, p = 0.53				

*Characteristic of respondent is statistically associated with their knowledge or training in economic evaluation

3.4 Discussion

Only 37% of clinical decision makers reported that they were aware of the decision-making process in the Ghanaian health system. Most respondents felt existing processes were not transparent (61%), were unfair (59%), did not consider the opinions of stakeholders including themselves (67%), and also did not ensure the appropriate use of public money (52%).

Respondents' awareness of the decision-making process was significantly associated with their primary discipline, current role and the level of care they worked at.

For the purposes of this discussion, it is assumed that factors recommended by clinical decision makers are what they would have considered if they were in a position to do so. From the results of this study, it is apparent that clinical decision makers attach more importance to clinical issues such as benefit to patient and disease burden than economic and cost effectiveness issues for decision-making, even though there were some differences in rankings of different categories of health workers with respect to their role and level of care where they work. This is comparable to the results reported by previous studies (5, 6, 124, 127, 137).

The factors considered as most important for decision-making were disease burden, diseases of the poor, population group to benefit and geographical area (equity of access). These results are similar to those in a study of Thai decision makers whose roles are different from those in the current study. However, respondents in this study did not make direct policy decisions but were implementers of such policies, while 42% of decision makers interviewed in Thailand were policy implementers (hospital directors and health workers) and 39% were policy makers (6).

However, while the Thai decision makers attached more importance to equity considerations in making decisions, clinical decision makers in this study did not regard it as so important (its relative importance was five out of 10), even though they considered the current process as unfair. This therefore raises a question of how "unfair" was interpreted by respondents of this study. It could be that their responses referred to every facet of the decision-making process. Another explanation for this result is the fact that clinical decision makers may attach more importance to other factors than 'equity' or 'fairness'. That said, it is worth mentioning that respondents perceived it as the least important factor currently considered by policy/decision

makers in the health system, hence giving it a 'five' may be seen to be a recommendation for its elevation in the current hierarchy of decision-making factors.

Also, as reported in previous studies (128, 132, 138), clinical decision makers considered the burden of disease an important factor for health decision-making. Pharmacists interviewed in the UK were of the opinion that factors such as severity of disease and burden of treatment for the patient and target population were important in making decisions, findings which are comparable to the recommendations made by pharmacists interviewed in this study (128, 138).

Contrary to the findings of Gallego et al. (134) and Williams and Bryan (132), clinical decision makers did not attach much importance to the safety and cost effectiveness of a health technology in making decisions. The reasons for this difference are not entirely clear, nonetheless, the differences in the decision-making roles of respondents and their knowledge and understanding of what those variables are could have contributed to that. Also, while hospital administrators interviewed in Australia considered the overall budget impact (126), Ghanaian clinical decision makers do not consider it as important. The differences in their responses can be attributed to the fact that health administrators make decisions on resource allocations, hence, are more likely to consider the impact of a particular decision (such as adoption of health technology) on the overall budget. Clinical decision makers on the other hand do not bear such responsibilities, but rather focus on the quality and effectiveness of patient care, hence, are more inclined to consider the factors that will help them achieve that rather than cost considerations.

In answering a question on stakeholders involvement in the decision-making process, these respondents were of the view that politicians, heads of institutions, health managers and expert groups were those currently making decisions, in descending order. Even though these are perceptions of those who do not make decisions, the factors identified are similar to some of

the findings reported in the literature. Health managers in Australia interviewed reported political pressures as factors influencing the decisions they made in the health system generally (122) and in adoption and uptake of new technologies (134). Iglesias et al. (5) also reported political considerations were major factors in health decision-making in Latin America.

The respondents in this study, however, recommended that physicians, health managers, expert groups and nurses be involved in the decision-making process (in descending order). Their responses suggested that politicians and health economists should not be involved in making decisions concerning the health system. This has implications for the introduction of HTA, as their non-recognition of health economists as influential stakeholders in the decision-making process would influence the acceptability and implementation of HTA findings. The reasons for the non-recognition of health economists as persons who should be influencers of decisions is not entirely understood. It may be that respondents are not familiar with who health economists are and what they play in the health system, as their roles are not currently defined. Respondents acknowledged the importance of involving consumers/patient groups in decision-making even though, the importance attached to them was not higher.

Lastly, clinical decision makers reported limited knowledge of and/or training in economic evaluation. This is comparable to what is reported by respondents in the literature reviewed. However, it was expected that the respondents in this study will have very limited knowledge compared to those in previous studies. This is because their roles were different and unlike in Ghana, the use of economic evaluation for decision-making was already occurring in the countries in most of the studies with the exception of those conducted in Latin America (5) and Thailand (2, 6). Those in policymaking roles are assumed to benefit from the findings of economic evaluation for making decisions such as resource allocation and managing budgets, hence, are expected to have more knowledge compared to clinical decision makers who do not make such decisions.

3.4.1 Strength and limitations of study

This study assessed the perception of clinical decision makers about decision-making practices, which fills a gap in the literature about what health system stakeholders at the clinical level think should be considered in this process. The results also provide information on how these type of decision makers, who are likely to use HTA findings, perceive the current decision-making processes and what factors they think should be considered, which is useful for future policies on decision-making. This is important because the outcomes/benefits of a particular decision are dependent on those who implement it: in this case, clinical health workers. Another strength of this study is that it assessed the relative importance of the factors and stakeholders that respondents considered appropriate to be involved in decision-making, which was not addressed in any of the studies reviewed on using HTA methods for health decision-making.

As with all studies, it has some limitations that are worth mentioning. The questionnaire required respondents answer all questions, respondents who acknowledged not having awareness of the decision-making process and those who were uncertain about the process still provided their opinions about what they thought were the factors considered and also who they perceived was most influential in the decision-making process. They also rated the characteristics of the decision-making process captured under their awareness of it. To address the latter, a test of association (which was statistically significant) was conducted between respondents' awareness of the decision-making process and the statements describing the characteristics of the process. The main difference between the two groups was that, those who were aware of the decision making process had more favourable view of the process compared to those who were not ($p<0.01$).

Secondly, as observed in the pilot studies, it is likely that some respondents may have still misinterpreted the ranking scale even though caution was taken to make it as clear as possible. To minimise the effect of misinterpretation of the ranking scale, it was explained to respondents orally during the face-to-face delivery of the questionnaire.

Thirdly, respondents were 'forced' to rank factors and stakeholders from the variables that were provided in the questionnaire. It may be that, there were factors they might have considered or felt should be part of the decision-making process that were not captured in the questionnaire. To minimise this, the variables included were from literature reviewed and respondents were provided with a wide range of decision-making factors and stakeholders involved in making such decisions: ten responses each.

Fourthly, the thesis acknowledges that there could have been a potential overlap of some of the factors, which could have affected the robustness of the ranking exercise. However, the findings from the thesis did not indicate respondents interpreting some factors as overlapping. For example while disease of the poor was perceived as the 3rd most important factor considered by decision-makers, equity was perceived as the least important factor considered by decision-makers. In addition, the thesis adopted a questionnaire that has been used previously and did not report this as a limitation. In addition, respondents from the pilot study conducted for this thesis to test the questionnaire did not report factors as overlapping. Therefore, the findings are true representation of how respondents interpreted the factors they were asked to rank in the questionnaire.

Fifthly, the number in each of the subgroups used to perform a subgroup analysis to identify the differences in the relative importance of responses of respondents was small; hence, may not have detected real differences in each group. Therefore, results from the subgroup analysis should be interpreted with caution. The subgroups being referred to here are different from the

two subgroups mentioned in point one. They include the primary discipline group under which there were medicine, pharmacy, nursing and others subgroups.

Lastly, the study assessed the perception of clinical decision makers about the decision-making practices of policy makers, therefore, the results may not reflect what happens at the policy level, and thus must be interpreted with caution. However, their recommendations could serve as useful inputs in developing resource allocation criteria in the Ghanaian health system.

3.5 Conclusion

This chapter has presented the perceptions of health workers about the current decision-making process in Ghana. It revealed that clinical health decision makers' expectations of how decisions should be made in the Ghanaian system different from what they perceive to be happening currently. Thus, there is the need for policy makers to consider these findings in their future planning and decision-making as the acceptance and buy in of clinical health workers will have an impact on the successful implementation of policies enacted. Health economists were the least preferred influencers of decisions after politicians, and this is expected to have an impact on the acceptability of HTA methods for decision-making in the Ghanaian health system as presumably health economists would have a key role in its implementation and use. Therefore, potential users of HTA need to be educated on the role of health economist in healthcare decisions.

Most of the recommendations by health workers seemed to be influenced by a focus on patient and population health rather than by economic considerations. This reinforces previous findings in the literature. However, it is expected that policymakers (decision makers at the national, regional and district levels), will place different relative levels of importance on some of the factors recommended by clinical health workers as their roles involve not only ensuring the wellbeing of patients and the population, but also managing and allocating resources and

administering budgets. Therefore, it is important to ascertain what policy/decision makers take into account when making decisions and also their recommendations on what factors could be included in the decision-making process to reconcile the differences for future planning. In addition, in terms of HTA, policy makers are those who will most likely initiate and lead HTA institutionalisation. They are also likely to use the findings of HTA directly, hence, it is important to also examine their knowledge and attitude towards HTA in the Ghanaian health system. This is investigated in the next chapter.

4 HTA IN GHANA: DECISION-MAKING PRACTICES, KNOWLEDGE AND ATTITUDE OF DECISION MAKERS AND RESEARCHERS

4.1 Introduction

This chapter examines the current decision-making practices of Ghanaian decision makers. The results provide useful inputs into planning for the introduction of HTA in Ghana. Knowledge about the specific decision-making context is relevant when a new criterion for decision-making is to be introduced. For this reason, decision makers at the national and district levels whose roles include making decisions on resource allocation for health service delivery were interviewed about what factors they consider and recommend for decision-making in the Ghanaian health system.

Further, the knowledge and attitude of decision makers towards using HTA to make decisions in the Ghanaian health system was assessed. This is important, since these types of decision makers are the potential future users of HTA. They are also better placed to initiate and lead the formalisation of HTA for health decision-making in Ghana than health workers. The potential barriers to the use of HTA and measures to address them were also explored. Researchers who are potential producers of assessments were also asked about their knowledge and attitude towards HTA. Thus, the main aims of this chapter are to:

1. Investigate the decision-making practices currently employed by Ghanaian decision makers and their opinions about possible improvements.
2. Assess the knowledge and perception of decision makers and researchers about economic evaluation and HTA.
3. Examine, from the perspective of decision makers and researchers, the factors perceived as barriers to the use of HTA in Ghana.

4. Examine, from the perspective of decision makers and researchers, the factors they perceived to be facilitators for the introduction and use of HTA in Ghana.

The next section describes the methods used in this chapter. Section 4.3 presents the findings in three main sub-sections; decision-making practices in the Ghanaian health system, the knowledge of HTA and perception about its use and the perceived barriers to HTA use and recommendations to address this. The findings are summarised and key issues highlighted in a final sub-section. In Section 4.4, the findings are interpreted and discussed with reference to the existing literature. Section 4.5 concludes the chapter, relating the major findings to policy implications.

4.2 Methods

A qualitative approach was used because it was anticipated that the knowledge and practice of HTA would not be widespread in the study setting; hence, some participants would have limited knowledge of the concepts. In addition, from the literature reviewed, it was realised that in settings where HTA was not used formally responses reflective of the general perception and knowledge of participants were more likely to be revealed using qualitative methods (2, 5, 6, 119, 120, 130). Therefore, a qualitative approach enabled the researcher to explain HTA to all participants, and also concepts and words that came up during the interviews that may have been new. The meaning and significance of their experiences with decision-making, and how it relates to this study were also explored.

4.2.1 Study area

The study was conducted in the Greater Accra region because the key government agencies that make decisions on health and health care delivery at the national level are located in the capital. These government agencies include the MOH, GHS and the National Health Insurance Authority (NHIA).

In addition to these government agencies, the health sector within the Greater Accra region is divided into six main districts, which are further divided into sub-metros or sub-districts. They are Tema, Ga West, Ga East, Dangme West, Dangme East Municipalities and Accra Metropolis. Each district is served by a district health directorate, which is overseen by a district health director. District health directors oversee health service delivery in their catchment areas by implementing policies made by the MOH and GHS. In all, there are 22 administrative health districts in the Greater Accra region.

4.2.2 Data collection process

Study population/sampling frame

The study population consisted of decision makers and researchers. For the purposes of this research, decision makers were defined as persons who are directly involved in health decision-making including rationing, selection of medicines to be listed as essential medicines for patient use at the health facility level and reimbursement under the NHIS. They also make key and strategic decisions in priority setting and allocation of resources in the Ghanaian health care system, where HTA could be applicable, and as such are potential users of HTA.

Decision makers are further classified into those at the national and local levels of the health system. While decision makers at the national level make decisions that affect every facet of the Ghanaian health system, those at the local level make decisions that apply to only their areas. In addition, they implement policy directives made at the national level. However, it has to be noted that while there is consistency in some decisions made by national and local level decision makers such as implementing policy directives, in other instances, they may be at variance. For instance, local decision makers may reallocate health resources dispatched by the national decision maker using an allocation criteria based on their judgement of where there is a need for such resources in their district, instead of how they have been instructed to allocate

them from the national level. Decision-makers were sampled based on their place of work and role description (see Table 4-1) stipulated under each title by their organisations.

Researchers are defined as persons who have knowledge about HTA or have conducted studies in the field, for example, health economists, epidemiologists, biostatisticians and clinical trialists. These individuals are classified as potential producers of HTA. Researchers were sampled based on their skill set which was identified through place of work and/or research publications. Table 4-1 illustrates the distribution of the study population and from where they were sampled.

Table 4-1 : Sampling frame

Study population	Sampling frame	Prospective departments/directorates	Eligible participants
Potential users of HTA			
Decision makers at the national level			
	Ministry of Health	Ghana national drug program, Policy planning, monitoring and evaluation, Procurement and supply, Traditional and alternative medicine	Directors Deputy directors Program managers Chief executive officer
	Ghana Health Service	Policy, planning, monitoring, and evaluation, Health administration and support services, Institutional care, Public health	Directors Deputy directors
	National Health Insurance Authority	Management, Claims, Provider payment, Research, policy monitoring and evaluation, Clinical audit and compliance	Chief executive officer Directors Deputy directors
Decision makers at the local level			
	Regional health directorates	Management, Pharmaceutical services	Regional health director Deputy director of pharmaceutical services
	District health directorates	Management of the delivery of health services at the district	District director of health services Municipal/district pharmacists
Potential producers of HTA			
Researchers	The University of Ghana, reviewed articles, snowballing	School of public health and other private organisations	Health economist Epidemiologist Biostatisticians Clinical trialists

Inclusion criteria

1. Decision makers within the sampling frame as defined above.
2. Researchers involved in work related to HTA.

Exclusion criteria

1. Persons that are not decision makers (with the exception of researchers)
2. Decision makers whose roles did not involve making health and healthcare delivery decisions.
3. Decision makers who did not work in the geographical area identified for this study.

Sampling and recruitment of study participants

A purposive convenience sampling technique was used to obtain the best representation of the population under study who could adequately answer the research questions[10]. In recruiting study participants for the in-depth interviews, the respective government institutions were invited, via a letter of invitation, to allow their employees to participate in the study. The letter included the sampling frame for the study to provide the heads of institutions with information about who prospective participants were. Once the institution accepted the invitation, prospective participants for the in-depth interview were contacted with permission, in person and through email correspondence, and were formally invited to participate in the study. Those who accepted the invitation were followed up through email, phone call or in person to arrange a convenient interview date and time. In this way, heads of institutions had no influence on which prospective participant was interviewed, as I interviewed those who agreed to participate in the study from the sampling frame.

[10] A purposive sampling technique is recommended for studies where the researcher seeks to answer specific questions, hence the need to identify a productive sample that could answer them. Convenience sampling also allows the researcher to select participants who are easily accessible (139). Due to the limited period of data collection, I conveniently selected decision makers who were in the position to contribute to my study objectives and were available to participate. For example, only district health directors who agreed to participate and were reachable were involved in the study.

For researchers, recruitment was undertaken using a snowballing method[11]. Initially, one health economist from the University of Ghana (who also works in the Department of Health policy planning and management) was identified through his publications and asked to identify other researchers (whose proportion is unknown) in academic and non-academic institutions who satisfied the inclusion criteria for the study. In the same way, those identified and interviewed were also asked to identify others who were contacted to participate in the study.

Data collection technique and instrument

A written information sheet and a consent form were given to participants to sign for their voluntary participation (Appendix 2, Document 3 for details). Data were collected over a period of three months (March to May 2016). To address an anticipated problem of misunderstanding of questions and concepts, a brief summary of the study topic was sent to institutions and study participants before the interviews (Appendix 2, Document 4).

I conducted all the face-to-face in-depth interviews using an interview guide (see Appendix 2, Document 5). The interview guide included open-ended questions under the following subheadings:

1. Current practices and/or criteria used in making decisions and researchers awareness of this
2. Recommendations to improve current decision-making practices
3. Knowledge about economic evaluation and HTA
4. Perceived anticipated barriers to the use of HTA
5. Perceived ways of addressing barriers and fostering the uptake of HTA

[11] Snowballing technique is used in instances where the target population is 'concealed', that is when they are few in numbers and hard to reach, as in the case for researchers in Ghana who do HTA. Hence, the researcher takes advantage of the social and professional networks of individuals by identifying one participant, who will then provide the name of other potential participants in their circle (140, 141).

Participants were interviewed separately at their workplace or in a place of their choosing to ensure privacy and confidentiality. All interviews involved probing of issues arising from open-ended questions and explanations of concepts regarding economic evaluation (EE) and HTA. They were audio-recorded and lasted between 30 – 60 minutes. Three interviewees preferred not to be audio-recorded and detailed field notes were taken for those interviews. The explanations given for refusal to be audio-recorded were discomfort and personal reasons that were not shared. Written notes were taken during all interviews[12].

Pilot in-depth interviews were conducted with four national decision makers, each from the selected government institutions to pre-test the interview guide. The pilot assisted with identifying and correcting unanticipated problems with the wording of questions. The pilot study revealed that in addition to providing interviewees with prior information on the study area (HTA), it was necessary to provide such information verbally at the beginning of the interview since some participants had not read the information prior to the interview. The results of the pilot study were not included in the main study[13].

During the interviews, an audit trail was kept to document the entire research process, pilot and main studies. It included all decisions made, experiences, recruitment of participants, reactions and emerging awareness of any assumptions or biases and the interpretation of each stage of the research. All assumptions and limitations of the research were acknowledged in the written research proposal presented for ethical clearance, before data collection. This was done to

[12] In conducting in-depth interviews, qualitative researchers recommend that written notes are taken irrespective of audio-recording to guide interviewer in the interview process as to what needs to be probed as well as explored in following interviews. The researcher is better able to reflect on his or her own thoughts if they are written down during the interview (142, 143).

[13] In addition to assessing the feasibility of the study, pilot studies enable data collection tools to be pretested for revision to ensure the tool is responsive to the research questions, as well as fit for purpose. Because data collection tools are often revised, it is important not to include data from the pilot study in the main analysis. However, the results of the pilot study can be reported on separately. Lessons learned and effect on the main study should also be reported (144-146).

identify the reflexivity and subjectivity of the study respectively (143, 147), and the extent of these in the final analysis.

4.2.3 Data analysis

Audio-recorded interviews were checked at the end of each day to identify emergent themes and to note when saturation had been reached. Recruitment ceased when no new issues were emerging. Interviews were conducted in English and transcribed verbatim by the interviewer. To guarantee the adequacy of interpretation, recordings were listened to repeatedly before and after initial transcribing to ascertain whether all responses had been captured correctly. Transcripts, field notes and audio-taped recordings were also given to a peer to crosscheck for any omissions or additions during transcription to minimise data loss and errors as much as possible (147).

Data were entered into Nvivo software version 11 Pro (148) for storage, organising, searching and coding. Neither the transcripts nor the analysis of transcripts was given to interviewees for feedback or comments. However, one participant was provided with the audio file upon request. The rest of the interviewees did not make such a request hence audio files were not shared with them.

An inductive thematic analysis was undertaken to ensure that the themes identified were strongly linked to the data collected. A widely used criterion for thematic data analysis developed by Braun and Clarke (149) was used as a guide to analyse data collected for this research, and for subsequent reporting. Table 4-2 presents the phases of thematic analysis as proposed by Braun and Clarke. The consolidated criteria for reporting qualitative research (COREQ) checklist (150) was also used to guide data analysis and reporting of findings. These guidelines ensured that having prior knowledge of what existed in the literature did not affect my analysis and interpretation of the results.

Table 4-2: Phases of thematic analysis

Phase	Description of the process
1. Familiarisation with data	Transcribing data, reading and re-reading the data, and noting down initial ideas
2. Generating initial codes	Coding data in a systematic manner and collating data relevant to each code
3. Searching for themes	Collating codes into potential themes and gathering all data relevant to each potential theme
4. Reviewing themes	Checking if the themes recognised correspond to codes identified. Generating a thematic map for the analysis
5. Defining and naming themes	Ongoing analysis to refine the specifics and redefine potential themes identified. Generating clear definitions and names for each theme
6. Producing the report	Description of themes in detail and selection of extracts relating back to the research question and literature to support the final write-up of findings of study

Source: Braun and Clarke 2008

Although coding was done by organising data under the objectives of this study (that is for this chapter), the main themes and sub-themes in this study were identified within the explicit meaning of the data. The interview transcripts were organised by place of work: GHS, MOH, NHIA and district level. Coding was done by first auto-coding each transcript[14] based on study objectives in Microsoft Word 2016 before data was transferred into Nvivo for further coding and analysis. Subsequent coding was carried out in Nvivo in a non-hierarchical manner for each transcript according to study objectives and place of work of study participants (to identify any differences in responses of participants who worked at different institution). Coding was done to capture keywords and themes emerging from the study. Coding was peer-reviewed by a fellow PhD student who is at the Faculty of Arts and Social Sciences of University of Technology Sydney with in-depth knowledge and skills in qualitative studies to ensure all data has been captured appropriately.

Emerging themes and sub-themes were organised for each subgroup (organised according to place of work) using coded segments of data. The themes were reviewed to ensure they were relevant to the coded extracts and the entire dataset. Themes and sub-themes under each

[14] Auto coding involves using headings and in Microsoft Word to organise your data under the subheadings in the interview guide.

subgroup were reviewed continuously to improve their specificity. The themes and sub-themes of each subgroup were compared, and then merged to produce the overall themes and sub-themes of the study. Initial thematic maps were made which were further refined through continuous analysis until final themes emerged. The themes and sub-themes were then organised in a hierarchical manner for reporting.

The notes taken from the three interviewees who declined to be audio-recorded were included in the main analysis which involved coding and derivation of themes. It is worth noting that the responses of these three participants were similar to those who agreed to be interviewed, and contributed to the generation of themes. In the presentation of results, information is supported with two or more quotes within the themes identified from participants. Further interpretation was undertaken by relating findings to the existing literature in the discussion section. The excerpts/quotes used were edited for easy reading and understanding without changing their meaning.

Data interpretation was made under the five subheadings developed for the interview guide (which was in turn derived from the study objectives) using the themes and sub-themes that emerged during the interviews. Data were interpreted based on the contexts in which they were collected. Also, the COREQ checklist (150) was used to guide data analysis and reporting of findings.

4.3 Results

Twenty-seven (n=27) decision makers and researchers were interviewed. Participants reflected the categories identified in the sampling frame; the only exception was that participants from the regional health directorate were not interviewed because of lack of availability during the data collection period.

Characteristics of interviewees

Fifteen of the study participants were males, and 12 were females. Each participant had been working at the institution and had held the same or similar position for more than two years. All participants had at least a bachelor degree. The three participants who declined to be audio-recorded were from the NHIS. A distribution of interviewees and their place of work are shown in Table 4-3.

Table 4-3: Distribution of interviewees

Institution	Departments involved	Positions	Total number
District Health Directorate (DHD)	Not applicable	District health directors (4), municipal pharmacist (1)	5
Ghana Health Service (GHS)	Policy, planning, monitoring and evaluation, Health administration and support services	Director (1) and deputy directors (3)	4
Ministry of Health (MOH)	Ghana national drug program, Policy planning, monitoring and evaluation, Procurement and supply, Traditional and alternative medicine	Directors (4), deputy director (1), program manager (1)	6
National Health Insurance Authority (NHIA)	Management, Claims, Provider payment, Research, policy monitoring and evaluation, Clinical audit and compliance	Chief executive officer (1), Directors (2), Deputy Directors (5)	8
Researchers (R)	Universities, research-based institutes	Researchers/lecturers (2), Program manager (1), Director of institution (1)	4
Total number of participants			**27**

The results[15] from the study are presented under two main headings, each with themes and sub-themes:

1. The decision-making practices (context) in the Ghanaian health system
2. The knowledge and attitudes of decision makers and researchers towards HTA

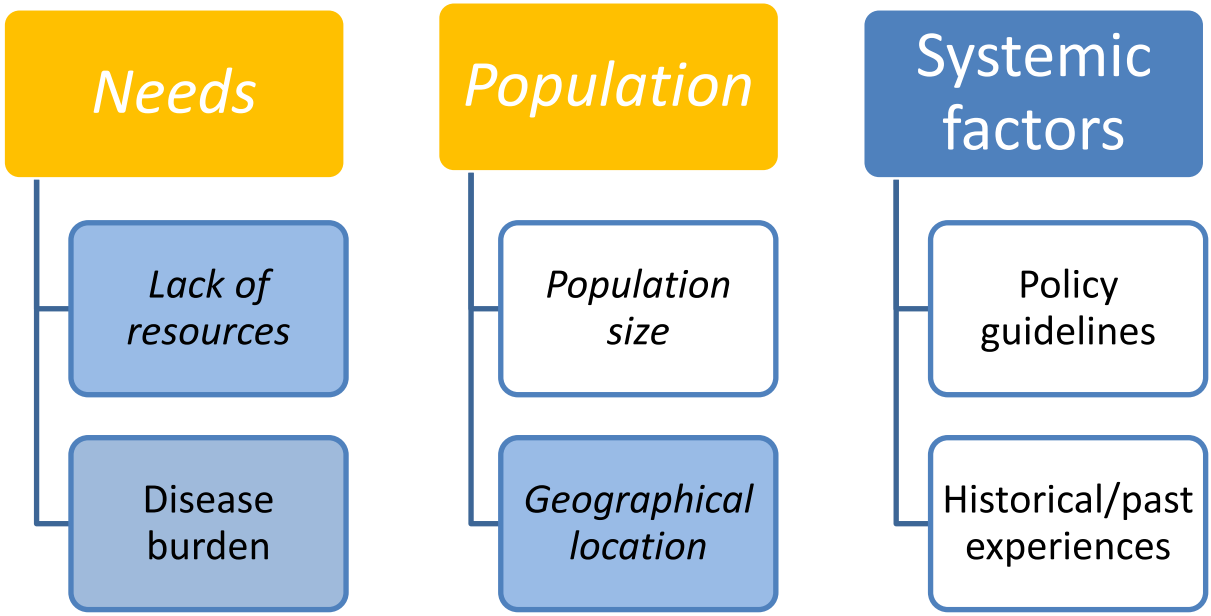
[15] In presenting some of the excerpts from the interviews, the word 'umm' indicates hesitation of the interviewee and (…) pauses in conversation or repetition of a word. A word in square bracket [ ] was used to explain further what the interviewee/participant was referring to in the interview but was not captured in the excerpt to promote reader understanding. Also participants were de-identified by using numbers.

4.3.1 The decision-making practices (context) in the Ghanaian health system

Decision-making practices are defined in this chapter as how decisions are made and what factors influence decisions.

Factors considered for decision-making in the Ghana health system

Three main themes emerged from the responses of interviewees, each with two or more overlapping sub-themes. The themes were needs, population, and systemic factors, and are presented in Figure 4-1.



The boxes at the top are the main themes, and the ones below are sub-themes. Themes and sub-themes that overlap with each other are identified with the same colour fill and italic lettering

Figure 4-1: Factors currently considered by Ghanaian decision makers for decision-making

Needs

The most prominent factor influencing decision-making has been themed as needs. Needs are what decision makers perceive as resources essential for delivery of health services but are

lacking in their district and/or catchment area. Needs were also described as health conditions that were viewed as a 'burden' that required attention in the form of setting targets to reduce the burden of disease, hence needed resources to achieve it. Diseases with a high burden such as those with higher incidence and prevalence rate, like malaria, were identified. Lack of resources and disease burden are interrelated in the sense that resources were seen as necessary to reduce a burden. Therefore, the theme 'need' is further divided into two sub-themes: lack of resources and disease burden. The next sub-section presents how decision makers perceived lack of resources as a need and how they made certain decisions in the health system about resource allocation.

Lack of resources

The ability to address the needs of the health system is dependent on the resources available. Thus, in expressing needs, decision makers identified what resources were lacking in a facility. They defined resources as medical equipment, human resources, finance and means of transport needed for production of healthcare and service delivery.

All district health directors reported that they allocated resources based on the needs of a particular population, town or health facility. For instance, it was mentioned that when medical equipment is received, such as such as thermometers, they initially distribute it to health facilities that did not have it, before considering those who have it but in limited quantity:

> *...Also, for devices like blood pressure apparatus, thermometers, stuffs like that; when they are coming they assign it per the district. So we look at who needs it the most and then we reassign it. (Participant 3)*

Similarly, when staff are assigned to their districts from the national/regional level, they are apportioned first to health facilities that lack that cadre of staff and therefore require their

services the most. One person described how staff are distributed to facilities in the district as follows:

> *...For human resource, when they post staff to us, we have to identify the areas where the staffs are most needed, and then we send them to the place. For example if I am given a community health nurse, I will post the person to a sub-district or CHPS [Community-based Health Planning and Services] zone, that need their services, and not the district hospital. (Participant 4)*

Some decision makers at the Ghana Health Service also mentioned that they took into account the need of a particular district or geographical area when making decisions. One participant whose role involved procuring and allocating vehicles and equipment had this to say:

> *In places like the northern part of the country where the area is big but have very bad roads, you can't get a vehicle to take all people everywhere for immunisation exercises. But if we have bikes, we can get ten people going to ten different places within a short time. So, I make the decision to procure bikes for them instead of cars. (Participant 9)*

Similarly, a district health director also explained that financial resources were allocated according to the ability of a facility to generate its own income to address its needs, in instances when two facilities have the same problem. This participant stated:

> *.... on the platform of generating funds if two health facilities don't generate funds, then I will look at the need itself. But if let's say Town A generate more funds hence is financially stable, I will let it [referring to health resources such as funding from the national or regional directorate] go to Town B. (Participant 1)*

Cost factors also influenced decision-making. At the national level for instance, some participants indicated that most of the time, there may be policies that are seen as beneficial to

the health system but they are not able to implement these; nor are they able to implement the accepted ones due to lack of financial resource. One participant said:

> *Of course, there are other factors that influence decision-making. We are looking at cost, do you understand? So you may have an idea, but is it feasible? Can we really do it considering the allocated budget? We face these issues, especially given the current situation where funds do not flow as expected. (Participant 7)*

Even though cost-related issues emerged from discussions with participants from the national level, district health directors did not explicitly discuss the issue of the cost of health technology vis-à-vis the available resources as an important factor that informed their decisions. For them, what mattered most was ensuring that their overall aim of better health for the populace was attained irrespective of the cost of achieving it. One district health director (DHD) expressed this in the comment below:

> *The pricing also informs us but very remotely, the first thing to look at is to cure the person, not to think of the cost involved. (Participant 2)*

The next sub-section examines disease burden as a challenging need influencing the decision-making process of participants.

Disease burden

Some decision makers stated that in setting priorities and allocating resources, the disease with the highest morbidity and mortality was considered as one with the highest need for resource allocation. These diseases were given priority over others. Two respondents, both at the national level, shared their views respectively in the following comments:

> *Well, it's [priority setting] dependent on the prevailing health conditions, the number one cause of outpatient attendance and death..., and then ensuring that women and*

children stay healthy. So those are the areas we look at to inform our priorities. (Participant 6)

For the benefit package, again we look at the disease burden of the country. Remember that Ghana national health insurance was actually a poverty alleviation mechanism, hence its focus of the burden of disease. (Participant 18)

In response to the burden of disease in Ghana, performance indicators are set at the national level, which are further redefined at the regional and district levels based on the type and severity of the disease burden. Performance indicators are goals set to monitor the performance of the health system according to its overall objectives. Performance indicators allow for monitoring of reduction targets of the disease burden and are mostly in consonance with attaining global directives such as the sustainable development goals for health. For example, each region and district are given targets to reduce infant mortality rates by a certain percentage. Therefore, in allocating resources, some participants described prioritising resources to indicators where they were struggling to achieve set targets, even if it meant transferring resources meant for other activities. A district director in a rural area said:

…When I look at my indicators and you brought me money to fund maternal and child health and I know that my ANC [antenatal care] coverage is really low in Town X. Despite the fact that Town Z has a lot of population, if their indicators are fine, I will let the money go to Town X. Because for me, it means Town X has more needs in terms of achieving the numbers for their performance indicators. (Participant 1)

This comment also suggests that a number of factors are considered during the decision-making process. Even though this participant mentioned population and need, the smaller town was chosen over the larger because the DHD perceived that achieving improvement in performance indicators for that district was more relatively important despite the smaller population.

These findings suggest that what is perceived as deficient in a particular setting, whether human resources or funding, influence decisions made by participants. In addition, the quest to attain nationally set targets to reduce disease burden guided participants in making resource allocation decisions.

Population

Another common factor used for decision-making at the national and district level that emerged from the analysis was population. Participants defined population as a group of people with a particular characteristic such as size, location, access to infrastructures like roads, water and electricity, disease prevalence, and type of health facilities available. They included populations served by a service, who inhabited a particular place or were affected by a condition or situation. The sub-section below discusses the subtheme of population size, derived from the overarching theme, and how this concept was used by participants in the decision-making processes.

Population size

The size of a population came across as the second influencer of decisions made by participants most especially when it came to allocating resources. Some decision makers at the national or district level indicated that they used this factor. Population size was described in terms of number of people who lived in a catchment area or attended a particular health facility or utilised a health service or were affected by a disease. For participants at the district level, resources such as for malaria control (for example, insecticide treated nets), are distributed from the national level based on the population density in each part of the country. Therefore, they redistribute these resources to the sub-districts. Participant 3 describes below how some decisions were made just by inferring from what was perceived as undertaken at the national/regional level:

Sometimes we receive monies and it is based on population. For instance, so Town P gets X amount relative to another district and the allocation is based on population density, so automatically, when we get such resources, it is implied that we also need to look at the sub-district populations and then allocate funds accordingly. (Participant 3)

In addition, DHDs acknowledged distributing resources that do not come with an allocation criterion from the national/regional level using the utilisation rate for that service. DHDs related utilisation rate to the number of people likely to benefit from the resource and to the efficient use of the resource. For instance, participant 4 suggested:

Again, umm, attendance is considered. I mean in terms of the number of clients that a facility sees. You also consider that. Because for example, Facility Z in Town W attends to a lot of clients, so if umm there should be an ultrasound machine to take care of our pregnant women, because of the numbers over there, I would want to put it there because they attend to a lot of antenatal clients. (Participant 4)

Even though this practice was admitted by only DHDs, in some ways, the thinking is still connected to the size of the population, which is also considered at the national level. It is also linked to a specific population that is likely to benefit from the resource, which is no different from what is done at both the district and national levels as admitted by16 participants as a decision-making criterion. For example, a national level decision maker explained that depending on the health resource available for distribution, which is mostly driven by annual targets, resources are given to facilities responsible for implementing the policy. However, the number allocated per district was also dependent on the number of that type of facility. This participant iterated:

Quite recently for example, we shared some resources that targeted lower levels and we used the number of CHPS facilities that are there because it was for CHPS

operations…which was in line with the health system's goal for primary healthcare. (Participant 8)

Another aspect of population that was considered by participants in making decisions at the different levels of the health system was the geographical location of the people and this is presented in the next sub-section.

Geographical location

A population's geographical location was considered by participants as their proximity to the national or district capital, which was also linked to access to basic amenities such as health facilities, potable drinking water and electricity. The farther away a population was from the district/national capital, the less likely they were to have these amenities. Therefore, they were considered as deprived areas, hence given priority over others in some instances. One of the reasons for this was attributed to the fact that often health workers refuse to report to such places when they are posted to work.

For this reason, the ability to access a town or facility via road was cited as one criterion considered when allocating resources in the districts:

And if it is funds, we again look at the population and then we apply certain factors like hard to reach areas, how difficult the terrain is. All of that come into play when we are allocating some resources. (Participant 3)

Access to health services and basic amenities due to geographical location of a population was also described by some participants as equity issues. They defined equity as distributing resources to populations that needs them most. Therefore, they were more inclined to assign resources to areas that needed them most or were the most resource-deprived. Equity criteria for decision-making overlaps with assessment of needs in terms of resources absent in that area. Other participants admitted to allocating resources equally among the population

irrespective of their needs. However, one of these participants who works at the national level perceived equality is as equity as presented in the excerpt below:

> *....it depend on the projects and programs of the Ministry for the year, otherwise, it's equity. If you have this resource and you have so many children [referring to number of regions, districts, and health facilities) as much as possible you share it equally among them, so those are the two basic things that inform our decisions on resources allocation (Participant 15)*

The study results discussed above suggest that different aspects of the population (that is their size, particular need, diseases or location) are considered as decision-making criteria for participants in their line of work. The next section describes the third theme that emerged in relation to decision-making.

Systemic factors

This theme concerns all factors inherent to the health system including policies and norms that inform decision makers in their day-to-day work. They include policy guidelines, past/historical experiences and politics. Participants defined systemic factors as those entrenched in the health system that one had no option but to comply with. They added that some past experiences derived from the health system informed their current decisions. The sub-section below explains how national and international policies on health remotely influenced decisions made by participants in the Ghanaian health system.

Policy guidelines

Participants defined policies as guidelines developed either at the national or international level concerning the delivery of health services. According to participants from the MOH who are directly involved in enacting health policies in Ghana, national health policies which inform all decisions in the health system are formulated considering global directives and commitments made by the country:

I know… the criteria for assessing what the sector's priorities are is based on evidence and also based on what we have signed onto globally. Like the Sustainable Development Goals and the Africa Union agenda 2063 which we have made some commitments to achieving. (Participant10)

There is a criterion called selection of medicines as defined by the WHO. As a country we have subscribed to essential medicine concept and having subscribed to that, there are methodologies for selection of medicines that we abide with. (Participant 11)

Other participants who were not from the Ministry of Health confirmed that national policies guide the allocation of resources and formulation of other policies to a greater extent. Some lamented the uncertainty surrounding the allocation criteria used. They were of the belief that resources distributed from the national level were based on activities developed from the national health policy for each year, called the program of work.

…. the criterion that is used is not really known, because we've been trying to push them to let us know what the resource allocation criteria are. They've not been forthcoming on it. So really, it's more of an activity-based thing sort of, they look at the various activities in the program of work and then they sort of allocate the resources accordingly. (Participant 8)

The results also suggested that targets were set for the year based on national policy directives and indicators. In the view of some, a proportion of resources were allocated based on directives of the regional health directorate and also from the national level.

The next thing is that, the parallel programs like malaria and tuberculosis, resources that comes from national and region comes with a spreadsheet as to how to spend the money so you do accordingly (Participant 1)

Malaria and tuberculosis are part of the burden of disease in Ghana, hence activities towards their reduction are developed at the national level with inputs from donor partners who fund health programs. Hence, resources assigned to them are specific according to the case loading in different parts of the country and resource allocation is informed by reports from previous years. The next sub-section expands on the influence of past experiences on decision-making.

Historical/past experiences

Participants defined historical experiences as decisions taken in the past that inform current ones. Four DHDs indicated that when allocating new resources, they took into account the resources that were allocated or used by a particular health facility in the previous year. Also, eight participants at the national level added that policies and guidelines were driven by what was achieved in the previous year vis-à-vis the overall national health policy. The same processes occurred at the district levels. Some participants explained the situations at follows:

> *.....so what we did was put the facilities in the spreadsheets and based on the past records of the request they brought to the district health directorate, we fix them in the spreadsheet. We also compare it to what they actually requested verbally, what they did and together we know that they spent X amount of money so we will give them that same amount. (Participant 1)*

> *We have guidelines but over the years based on our performance, then our priorities change, so we have priorities as to what we want to achieve, and then set targets and allocate resources accordingly. (Participant 6)*

Other decision makers added that in the past, every political party that had come into power had implemented policies stipulated in their manifestos. Therefore, as a decision maker, these are considered in the long-term planning and implementation of policies, as the differences in

the political ideologies of the ruling parties influence policies that are pursued (allocated more resources) among the overall national policies.

Despite widespread reporting by most participants on the use of either policies or lessons learnt from previous practices in the health system to guide decision-making, some alluded to the fact that some decisions were made on ad hoc basis without any predefined criteria or consideration of factors. Decisions were made based on what was at stake as perceived by the decision maker:

> *So if you are a head of unit and you have a problem with let say your air conditioner, and say the minister's own is broken down today, definitely we will attend to that of the ministers'. Or even me as your director, if mine is broken down and yours is broken down; yours may have broken down before me but definitely I will make sure I attend to myself, then after that I will see to yours. (Participant 15)*

These findings imply that decision makers are also guided by other factors characteristic of the health system, some of which are policies that needs to be adhered to and others are from experiences that are learnt over time in their line of work.

Factors recommended for consideration in making decisions in the Ghanaian health system

Following their shared experiences in decision-making, participants were asked in follow-up questions to make recommendations on what they perceived as important factors to be considered in the health decision-making processes in Ghana, irrespective of what they were doing.

As seems to dominate the current decision-making processes in the Ghanaian health system, participants suggested the importance of assessing the needs (mainly challenges and resources needed to address them) of the health system and population and enacting policies that would address these needs. These priorities were expected to drive the yearly program of work, which when delivered was anticipated to improve the health of the populace. Needs were expressed

mainly as the burden of disease of the population and resources that were lacking in the health system as explained in the previous sections. Some participants lamented that some current decisions especially on resource allocation were driven by donor agency preferences rather than the country's needs and it was necessary to change this:

> *We need to assess and consider the services that will promote health, possible gains in health vis-à-vis those that are very catchy tropical diseases but affect only a few and mostly maybe not the neediest. For instance, if you look at the allocation of resources in terms of HIV, malaria and tuberculosis from the Global Fund, it constitute majority of overall health spending even though it doesn't address the disease burden of the country. To me, it doesn't make sense and has to change. (Participant 19)*

Participants also maintained that every aspect of population (size, location, specific needs, disease and services) was a relevant decision-making criterion in the Ghanaian health system. In addition to the characteristics of population that currently informs decision-making in Ghana, decision makers also suggested that the poverty index of a particular population group, instead of their proximity to the national/regional/district capital, be considered:

> *I think they can look at umm, poverty index sort of people. Look at how poor these people are in terms of you know access to cash. Umm, at national level I dare say that in allocating resources, they will say, 'oh Greater Accra is the capital, we are in Accra, so resources do not come to us'. However, there are pockets of people in Greater Accra who are less resourced or poorer than certain people in the rural areas. Yet still, they will send it [resources] to other regions that are further away. (Participant 3)*

Lastly, in addition to the factors decision makers were currently using, they perceived that other criteria that would ensure more efficient use of health resources be included. Some participants

expressed these as methods or criteria that would ensure that resources available were assessed and considered before budgeting for a particular year:

> *I think umm… we don't budget for the purpose of budgeting. Before the budgets are approved, the government must ensure the monies are available so that once we go through the process, we won't award contracts only to be told there is no money and then if you are not careful you land yourself in judgement debts. So I think we must program our activities in such a way that monies budgeted for are actually available. (Participant13)*

In addition, other participants equally recommended methods that would provide decision makers with the necessary information to be able to choose between alternatives:

> *When it comes to cost and availability and even options, there is no real scientific way to weigh drug A against drug B or to decide to take out drug B and use drug A. It is all umm, about what feels comfortable for us, you know, in our setting and so that could be improved. We need a method that will enable us to make such choices so as to improve the efficiency of the health system. (Participant 5)*

Some decision makers at the national level also recommended that the financial impact of any health technology be assessed before its adoption and funding:

> *We need to put the committee in place and they will periodically update and look at the issues. All the issues that we need to include, they look at them, which one is number one. They need to consider the funding we have to see if we can include something else. I mean weigh it and see how the funding compare to the income, how expenditures for interventions compare to the health budget, is working well. We need to know the impact of funding intervention X on the health budget. (Participant 8)*

On the contrary, some decision makers at the district level thought costs and affordability of health technology should not be criteria on which decisions are based. They were of the view that, once there was an established need for a health technology, it should be provided irrespective of the costs:

> *Costs should not be driving our decisions. I believe in ensuring the wellbeing of the populace irrespective of the cost involve. Once the population needs a drug or equipment, the government should provide it. They shouldn't say it is too expensive so they can't, while they are spending all these monies of unnecessary things; a healthy nation is a wealthy one. (Participant 3)*

These results suggest that decision makers consider most of the factors currently informing decision-making in the health system as relevant, and should therefore continue to be considered. They however acknowledged the importance of adding economic issues such as efficiency and financial implications as a decision-making criterion in the Ghanaian health system.

Section conclusion

Overall, according to the participants in this research, what is currently happening in the health system is that decisions are made considering a number of factors such as needs, historical experiences, guidelines (both national and international) and population characteristics. However, no particular order/guideline is followed. Criteria that are deemed important at a particular point in time are used; and decisions are sometimes made on case-by-case basis.

In terms of recommendations, while some considerations such as the 'need' of the health system and the population were suggested for retention, new factors were also endorsed for consideration. One recommended factor that is not frequently used was pursing efficiency by assessing the opportunity cost of one decision compared to the other, and the financial impact

of that decision on the health system's available resources. These issues are among those explicitly addressed in an HTA process.

The next section explores the attitudes and knowledge of decision makers and researchers regarding HTA.

4.3.2 The knowledge of HTA and perception about its potential use

This section presents the knowledge of decision makers and researchers about economic evaluation and, and their perception about its potential uses in the Ghanaian health system.

Knowledge and perception of HTA

Twenty-seven participants were included in the analysis. While a majority of participants reported having knowledge about EE and HTA, less than a third either had a health economics background or had been exposed to a form of training or workshop that dealt with it. The knowledge of EE was more widespread compared to that of HTA. Participants defined HTA as an extended form of EE where financial impact analysis is included. Most of the participants' knowledge of HTA was very basic: its definition and possible uses. The knowledge and lack of knowledge were found at all levels of decision-making, national and district, as well as among researchers.

Of the participants with no knowledge about HTA, some associated HTA with the use of mobile phones, computers, telemedicine and technological innovations in health:

> *What I know [about HTA] and of course just recently, about last year or so we came out with umm mobile device; a technology policy, the one we use a mobile phone. We are into it, and we find it very useful. (Participant 7)*

Listening to even the way the wording goes, we want to assess the health industry to see whether we are taking advantage of technologies to advance our process. (Participant 13)

In addition, according to a researcher:

HTA involves using technology like a mobile phone or something in the health system. (Participant 21)

The construction and understanding of the word 'technology' by participants can be associated with what they are exposed to in their line of work and their general knowledge about technology. The daily roles and interaction of interviewees with some particular form of technology could have also informed how the meaning of technology was construed. It consequently translated into how some decision makers perceived its definition and focus of assessment.

It is not surprising that a participant with little knowledge in HTA, and whose job description included administration, management of transport, and distribution of resources such as beds, indicated that the definition of 'health technology' and 'HTA' as such was not appropriate. This participant suggested that the word "technology" be restricted to hospital beds, equipment and medical devices only and not to medicines and procedures:

...Some people came from the UK recently and said they were here for health technology assessment, but then, they were actually assisting us come up with the essential medicines list and those kinds of things. I don't see what health technology

has got to do with that [essential medicines]. So personally, I don't know what the whole thing is about. (Participant 15[16]).

..... Because if it is essential medicines and you are helping people to determine which are the essential medicines and how to go about procuring and those kinds of things, I don't see where health technology comes in. So that is my understanding. (Participant 15)

When asked a follow-up question about the understanding of health technology, the same participant replied:

I think that health technology should be hospital beds, hospital equipment. How they work best and that kind of things; they break down, and you are repairing them; that kind of things. If you ask me about health technology, that's what I think it should refer to and nothing else. (Participant 15)

However, this participant was willing to embrace a broader definition once it was understood that the definition is globally accepted and used:

If it's an internationally accepted standard and definition that we use to do these things, I have no objections to it. As you are saying, it has good sides, that is why, and it is good to have standards for everything, that's the basis. Moreover, the more globally accepted those standards are the better. (Participant 15)

Generally, HTA was generally perceived as another software/tool/method used for making decisions such as those concerning resource allocation in the health system. For some participants HTA is a method or scientific way of making decisions in the health system. These

[16] This participant had been part of a contingent of Ministry of Health directors who were briefed on the initial findings of the pilot HTA on anti-hypertensives, which was carried out by NICE international.

participants perceived any way of making decisions that uses scientific evidence for making decisions as valid:

> *Well it sounds to me like a very scientific way of doing things and immediately I will say even without any hesitation, oh yes, the scientific methods, anything that is done based on science, is evidence-based and you can trust it. (Participant 3)*

Other participants also considered HTA as a tool. This study identified that a 'tool' was a method or technique that participants understood to be of use in decision-making:

> *I believe that HTA is a tool; a very valuable tool that we can use umm to make decisions and prioritise our needs. (Participant 4)*

Perhaps participants were used to computer software programs where routine data was entered to generate results, such as in the case of the District Health Information Management System (DHIMS) software program, hence associating HTA with what is commonly known as another software/tool/method used in health care delivery.

The findings suggest that knowledge about HTA is limited and participants have different understandings of it. The next section discusses participants' suggestions for the prospective uses of HTA in Ghana.

Potential uses of HTA

Most of the participants acknowledged the value HTA can potentially add to the Ghanaian health system. Views on potential use for HTA varied among participants. For some participants, HTA was perceived as a means of justifying the use of public resources and giving legitimacy to decisions, amidst the pressure from some manufacturers' on the government to adopt new technologies.

...there is a lot of political pressure and other things for a new technology for reading rapid diagnostic tests for malaria to be adopted. Meanwhile we don't know what extra benefit it will bring. And I have heard that the insurance [NHIS] are even talking with them to adopt it. So, this is where I think HTA comes in, to resolve some of these controversies. I mean going forward, there is going to be more of these so there is a need for justification of investment. (Participant 8)

Others also suggested that HTA could be used for setting standards for conduct, allocation of scarce resources, ensuring value for money, and containing cost.

I think such an assessment is long overdue. We really need it. If you look at the way we operate, we are never able to raise as much money as we need for our activities. That makes it very, very important that we are able to prioritise by taking advantage of assessments such as HTA that will help us to make the best use of our very scarce resources. (Participant 13)

I believe that in a resource limited country like Ghana, it will be a very effective and useful tool to use in making decisions to choose the various options that we have, umm when making decisions on how to spend money on health care. HTA can assist us save cost and promote patient safety. (Participant 4)

There were also varied opinions about using HTA for decision-making in the Ghanaian health system as a whole and at the different levels of care and to what purpose. A small number felt the country was currently not in a position to make choices between interventions. Those participants indicated that all interventions were equal and complemented each other hence did not perceive the need to choose between two or more competing alternatives.

> *… it's an industry [health service delivery] that we hardly have the luxury of alternatives to choose. …Most at times, you have to apply all the options… So, it is about which option you are choosing at what particular time. But there is no luxury to drop any of the options. They are complementary options. (Participant 6)*

Likewise, a few decision makers at the district level saw prioritisation and rationing of health resources as unfair. They recognised its importance only at the regional and national level and for making high-level decisions such as building hospitals:

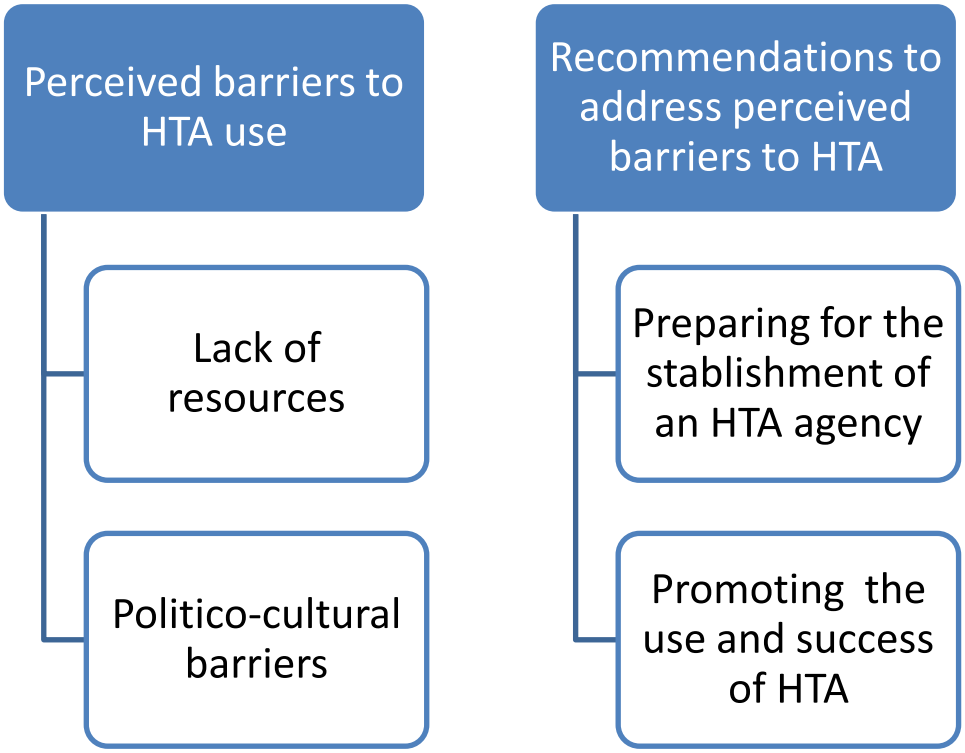
> *….I have had some sort of training in economic evaluation but I don't think it is applicable in our core business now because, it's looking at efficiency of drugs, efficiency of utilisation of resources to the best optimum use. But we haven't gotten there yet so I've also put it aside. It's those at the regional and national level who needs it to make decisions on hospitals and what not. For me, we are now building out the system so we cannot afford to use it [economic evaluation]. …I have taken the facilities as all my children, if I need to feed, I feed everybody at the same time, so if this one needs A, I provide all the five facilities with A. Therefore, using it [economic evaluation] to decide who should get what will be unfair. (Participant 2)*

These findings imply that while majority of the participants perceived HTA as an assessment approach worth pursuing, some did not. Those who did not perceive HTA as an assessment worth pursuing felt Ghana could not afford to be making choices between different interventions; others felt it could be done at the higher levels of the decision-making process, such as at the national and regional levels.

4.3.3 Perceived barriers to the use of HTA and recommendations to address them[17]

Following their suggestions for the potential use of HTA in the Ghanaian health system, participants were asked to discuss what they anticipated as barriers that could hinder the use of HTA and to suggest measures to overcome them. The findings presented here are for both researchers and decision makers.

Two overarching themes emerged for both the barriers to the use of HTA and recommendations to overcome them. The barriers were characterised as resource constraint and politico-cultural factors, while recommendations included setting up an HTA agency and fostering the use and success of HTA. Figure 4-2 illustrates the identified themes and sub-themes.



The boxes on top are the main themes, and the rest are sub-themes

Figure 4-2: Perceived barriers to the use of HTA and recommendations for addressing theme

[17] The definition of HTA, the methods, appraisal process and uses were explained to each participant before they were asked about perceived potential barriers to its use in Ghana and recommendations to address them.

Lack of resources (and recommendations to address them)

The participants identified that Ghana lacked the required resources in terms of data, human and funds, to undertake HTA. Participants defined resources as the basic requirements for HTA. For ease in reading and understanding, the barrier 'lack of resources' is presented alongside measures recommended to overcome this. These recommendations were suggested as important in the preparation for and setting up an HTA agency as well as using assessment findings for formal decision-making in Ghana.

The issue of insufficient data as a barrier was raised by a number of participants. Data was believed to be inadequate and fragmented. Researchers were of the view that the limited data available were inaccessible and not in usable form.

> *You don't know whether they are holding on to it or lack of capacity to manage the data. There are people who have all the information on their laptops. If you want that information, that person has to be there to open his laptop and be willing to give you that information. So there are three things: either we are not keeping it or we keep it and we don't want to give, or the format you have is different from what you are expecting. Sometimes you go to facilities and you want simple data and some have lumped everything together, meanwhile, you are interested in the disaggregate. (Participant 24)*

On the other hand, DHDs and participants from MOH and GHS referred to their ability to access a database referred to as DHIMS which informs annual reporting and decision-making. However, some acknowledged that all the data were not in one place for easy access, which posed as a major challenge for usage in HTA.

> *....so, the data is there, but we realise that the main thing is that, they are in a lot of places; they are very disorganised. So, it's going to be a major challenge for us. Being*

able to get data from places that we should have them and extracting the data and having to organise them before we can use them, that's going to be a major challenge. (Participant 12)

However, one thing that all participants agreed upon was the unavailability of skilled personnel to collect data, which consequently reflects the poor quality of the available data. Unskilled persons were defined as people with basic education and no training in data collection or information management:

Another thing that is currently a problem is the quality of data is poor. So we are going to face a challenge of data, our data management is too poor. Starting from data collection to collation to storage is poor, so it is going to be a disaster. Also, we are dealing with non-skilled people collecting data, which is even a bigger problem. (Participant 18)

We have an issue as a country when it comes to data collection and management. This is because, the very people who collect the data do not have the needed skills in data management. Some don't even understand the relevance of the information they are collecting from patients, therefore, do not invest time into it. There are a lot of errors and missing data in what we have due to such people. (Participant 8)

To address data-related barriers, several suggestions were made by participants. Proper data management was suggested as important for the conduct of HTA. Also, mentioned by participants, especially researchers and those from the NHIS, was the development of a standardised data collection tool that captures all the necessary data needed for HTA and other health services research. They also highlighted the importance to standardised and collate data collected at all health facilities in the country.

In addition, they recommended capacity development to ensure quality data collection. After data collection, adequate data management including collation, processing and storage were mentioned as relevant to foster the use of HTA. Researchers, in particular, highlighted the need to make data accessible to everyone to facilitate the conduct of research and other HTA activities:

> *So health information system is very key, and that is why we need to strengthen that because without evidence base we cannot do anything in HTA and that might call for revisiting the way we capture our database and streamlining them so that we can answer the questions we want to answer. (Participant 10)*

Another barrier frequently cited by participants was the lack of appropriate human resource capacity to undertake HTA. All participants emphasised the need to address the issue of human capacity if indeed HTA is to be pursued in Ghana. However, the extent to which human resources were perceived as a barrier differed among participants. The majority of participants stated there was limited capacity or no capacity at all:

> *I also see that our capacity, people who really know how to conduct an HTA is limited, so it would be a challenge because to have a good assessment done, you must have people who have the capacity to do that and I don't believe we do have that kind of technical capacity, so that could also be a challenge. (Participant 5)*

> *I have not come across any Ghanaian yet who knows how to do that [HTA]. Therefore, this is one big challenge we will need to address. (Participant 18)*

Conversely, a small number felt the capacity was available and needed to be developed further.

> *I think that we have the capacity for some of these areas. As I said, we have to bring together different pieces of evidence. I think some of the clinical evidence; the country*

has the capacity. Even cost effectiveness, I think we have emerging capacity, but I would not say we have the sufficient capacity. (Participant 23)

To address limited human capacity, participants in the present study recommended building human capacity in all areas concerning HTA:

....so if we are looking in that direction [HTA], then we need to develop the skills. We have young people who are very good with Excel and all those things, who can be trained to do the work. Not those people who are sitting at the ministry attending the workshop and think they can, they know HTA and making noise about it. We need to train the personnel who will do the actual work so that their outcome will be credible and we can use it to make decisions. (Participant 17)

In addition, some participants suggested developing skills through collaborations with other countries with the technical skills in conducting HTA while Ghana trains new people.

We do not necessarily need to start from scratch. We need HTA, and we need it now. So, we will benefit as a country by working with these countries that already do HTA. In that way, we can learn from them and start using HTA while the people we send out there to study how to do HTA are learning everything afresh to come and add to the capacity. (Participant 23)

Lastly, resource contraints preventing the establishment and conduct of HTA were also perceived as a barrier by participants. There was a consensus that current funds for healthcare were limited, and therefore allocating some for research and appraisals was going to be a challenge:

On the side of policy makers, the first barrier will be they will think that the money they have is small to even allocate some for research. So that is the first challenge, so until

you get somebody who thinks research is important, that is already taken away from the whole thing. (Participant 24)

So, there will be other financial barriers, even to set up a team to work on this. To find money to do all these studies to provide the evidence, the money will just not be forthcoming, and that will be a problem. (Participant 22)

When asked how the funding barrier can be resolved, participants recommended that the government make a financial commitment towards HTA to ensure continuous funding for its activities. A national decision maker recommended:

...a budget that is approved by the government; a budget line for these evaluations. It becomes law if government and parliament, umm cabinet approves and becomes more or less a policy that binds those who are in charge of resource allocation, et cetera then they will have no option than to put some money there. (Participant 7)

These findings imply that participants perceive that the data, human and financial resources required for establishing HTA in Ghana are not currently available. To be able to pursue HTA, making data available in the required format was recommended by participants. Perhaps the formulation of a data policy that captures all the data needs enumerated above would ensure effective implementation of HTA. Participants also suggested developing human capacity, and allocating funding for HTA. The next section discusses how participants perceived politico-cultural factors as potential barriers to HTA.

Politico-Cultural barriers

Politico-cultural barriers are those perceived by participants as factors inherent in the health system that are likely to hinder the introduction and use of HTA in the Ghanaian health system. Under this theme, the barriers are presented as part of the political and cultural environment.

The measures suggested to mitigate the barriers are presented under the two main themes that emerged for recommendations to promote HTA introduction and use as shown in Figure 4-2.

Political environment – barrier

Politics is defined in this context as the influence of a political party either in government or not, and other forces external to health system such as the media. The participants perceived political interference as a potential barrier to the use of a rigorous and evidenced based decision-making criterion such as HTA where findings may not suit a particular political agenda:

> *In health policy, political will is very important. So umm, to get politicians to accept it [HTA] as a methodology to bring in efficiency to the processes [decision-making] is also going to be a challenge. Especially if some decisions do not align with their campaign promises and political agenda. (Participant 21)*

The role of the media in discussing technologies under assessment while a decision about funding was not yet made, especially ones that affect a particular population and/or are perceived as controversial, was also perceived as a potential hindrance to the use of findings from HTA:

> *...we may have to make some hard decisions sometimes that may be unpopular with some people. For instance, we may choose one medicine over the other based on some evidence using HTA. In Ghana, we often get political interferences in some of these things. Especially based on a lot of media communication about it that pressurise politicians to interfere. (Participant 12)*

The potential for the cultural practices of the Ghanaian health system to hinder the establishment of HTA is presented in the next sub-section.

Culture of the health system – barrier

Culture is defined in this study as individual characteristics/attitudes, ideas, customs, and the accepted way of doing things in the health system. These include ideological issues, individual characteristics and interests, and established practices. Accepted ways of doing things may either be codified in written documents (such as policies, guidelines and protocols) or be non-written/implicit. Participants interpreted 'culture of the health system' as stakeholder/user interests, the historical way of making decisions in the health system and knowledge and understanding about different methods and criteria for decision-making such as of HTA.

The individual interests of potential users of HTA and other stakeholders in the health system were perceived by participants as possible barriers to the adoption and use of HTA. For example, the financial interests of some stakeholders such as pharmaceutical companies and other manufacturers and importers were perceived by a majority of participants as a major challenge. These stakeholders were perceived to be benefiting financially in the current health system, where no rigorous assessment was needed to appraise a health technology for funding by the government, hence their likelihood of resisting the introduction of HTA in Ghana:

> *I think one major barrier is having the major stakeholders accept it because the system as it is, I believe makes room for, umm, certain interests; people have financial gains to begin with, so when you are making such assessment and coming up with choices, you know, it is possible that some financial interest may be lost instead of gained and you can have a challenge there. (Participant 5)*

> *The whole thing is the personal interest of people. I mean people may not like to use it because of the stake that people feel they have in the system and what they think they will lose when HTA is introduced. Aha! Because in the absence of no criteria, people*

benefit and if you bring some stringent criteria people will feel they will lose out. (Participant 8)

The opportunity cost of conducting HTA was also seen as another barrier to the use of HTA. The day-to-day requirements of the health system such as electricity use and wages were suggested as justifiable use of health resources compared to HTA when resources are constrained. Many participants mentioned these competing interests as a barrier to the possible use of HTA:

I am also a health economist, who will do all the cost benefit analysis and all these things. You do them, and you have to place them on the table of the decision makers. Nevertheless, they are constrained by the decision you make; I mean because of other factors. The government will give you a ceiling of x million cedi, you use it to budget, and then you are given about one-tenth of that, what do you do? That is where the prioritisation comes in. So, you ask yourself is it worth doing this economic analysis when they are going to disconnect my electricity, I have to pay my water bill, I have to pay my, umm, cleaners and a whole lot of things like that? (Participant 7)

Another cultural barrier identified by all the participants was ignorance/lack of knowledge of the major health stakeholders about HTA, including its relevance to the health system and potential benefits. Participants were of the view that because of the lack of understanding of HTA, this could lead to decision makers resisting its introduction. They attributed the resistance to their ignorance of the potential benefits HTA could offer the health system:

It is the level of understanding of HTA and orientation of stakeholders of health will be an issue. For people to understand HTA, appreciate it, adapt to its introduction and use it is going to be a big barrier. How do we expect people to use it if they do not understand it? To me that in itself is a huge barrier. (Participant 6)

The last perceived cultural barrier to the use of HTA was the difficulty in changing entrenched ways of making decisions. All the researchers and many decision makers perceived the current ways of making decisions in the health system as a barrier. They argued this on the basis that individuals are comfortable with the ways in which they do things, and are therefore less likely to accept a new way of doing the things unless they are convinced of its possible advantages. Some participants also indicated that the current processes were over-reliant on global evidence and directives from global partners:

> *I think decision makers are not yet used to making decisions with this kind of evidence [HTA]. This is because the WHO has largely done it for them. They [decision makers] rely on the global evidence that has been gathered by the WHO to make their final decisions and recommendations. They have not been used to HTA; it is not part of the history of decision-making. This is a barrier in its self. (Participant 23)*

These findings suggest that participants perceive political and media interference as a barrier to using evidence derived from HTA for decision-making. They also implied that lack of knowledge of HTA by stakeholders and their entrenched ways of making decisions were a barrier. Other stakeholders (such as manufacturing companies, importers and pharmaceutical companies) perceived as benefiting from the current system were seen as those who will oppose the introduction of HTA in Ghana. The next section presents recommendations made by participants to address the politico-cultural barriers.

Recommendations addressing political and cultural barriers in the health system

To address all politico-cultural barriers, the two themes that emerged from recommendations made by participants were (1) preparing for the establishment of an HTA agency and (2) promoting the use and success of HTA. The former consists of all the factors/activities suggested by participants that address what should be considered and done before the

establishment of an HTA agency in the Ghanaian health system. This included addressing the lack of resources (human, data and financial). On the other hand, the latter concerns measures suggested by participants to be put in place to ensure that HTA would be used effectively and deliver the expected benefits.

Preparations for the establishment of an HTA agency

Before setting up an HTA agency and using it to inform decisions, participants were of the view that certain structures needed to be put in place to ensure its positive reception and use by the intended users.

To start with, all participants suggested the involvement of all stakeholders in the establishment of HTA. They perceived this as essential if the use of HTA for decision-making in the Ghanaian health system was to be formalised. They were of the view that people's participation in the process would guarantee their acceptance. The stakeholders mentioned included politicians, health workers, the public, pharmaceutical companies and donor agencies:

> *One thing that we know about this sector is that if you start doing something and you don't get the stakeholders sensitised early enough, you encounter resistance. So right from the word go, it's good to engage the relevant people … who are key players in this whole game [health system decision-making process]. Get them involved to understand what this whole thing is about, and how it can impact the work that we do. More importantly during the times in which we are working with very scarce resources. So once they understand how this can help, trust me, everyone will try to... umm... give it a push. So that is the best way we can introduce HTA. (Participant 13)*

In addition, to be able to establish an HTA process and use it for decision-making, participants suggested that some pertinent issues be considered during the planning and establishment phases. One of these would be the development of a policy framework to guide the conduct of

HTA and to make it mandatory. Participants were of the view that once HTA had legal standing, monies would be allocated to it and decision makers would be obliged to use assessment findings:

> *But I think if it [HTA] is made part of like the situational analysis before the planning then I think whatsoever funding is going into the planning process, HTA is part. Funding is given to it so that it can be done to inform the interventions that are put into the plans. But what I want to say is that for now, we don't have any policy framework that says that every activity you have to do that. So once we get a policy or law, its use will be made mandatory. (Participant 7)*

Also in preparation for the formal use of HTA in Ghana, some participants suggested that the country should define the meaning and uses of HTA in relation to what the assessments should focus on in the Ghanaian health system. They believed this would streamline the uses of HTA and also ensure everyone understands and adheres to its findings:

> *The thing is that, if it is defined as this and this and this, and we all come to agreement that this is the definition, then that is the end of the matter. There would not be any resistance in any way whatsoever. (Participant 15)*

Another issue raised by some participants concerning the setting up of an HTA agency was the appropriate place to site it. The location of the HTA agency was seen as a relevant factor if all health stakeholders are to accept and use the evidence generated from health technology appraisals. There was a consensus that the agency be as independent as possible. Participants recommended that the agency be in a different location from the Ministry of Health, the NHIS and any government agency with a direct interest in health service delivery:

> *I think we've come to a point where the question will be where this activity is housed and supervised. At the moment, I do not think the NHIS can incorporate it because the*

good thing about HTAs is independence and rigour. And if it were to reside at the NHIS, there will be a lot of backlashes because people will think it's self-serving. Now there is a push for it to be at the ministry. It comes with its difficulties as well. The moment it is owned by ministry and government, it brings a certain dimension of distrust. But if it's a body, be it you know a committee or whatever, where people are carefully selected, there is confidence in those people, I mean there is bound to be acceptance in whatever opinion they put out. But to make it a department of the ministry becomes a challenge. (Participant 16)

Still concerning preparing for HTA use in Ghana, the majority of participants suggested the appraisal team be carefully selected to ensure fairness of the process and acceptance of HTA findings. They proposed members of the appraisal team be people with no conflict of interest or political inclinations:

Another issue is that there must be impartiality to it [HTA]; that the people doing the assessment do not have the conflict of interest …I will even think that it will be good to have a separate entity that … has no interest in service delivery. Yes, like academia or researchers, then they are insulated from this, and the results are credible enough to be used. Yes, so I will rather go in for that. (Participant 8)

Some participants were also of the view that a commission or entity could be set up to undertake HTA appraisals. The minister for health was seen as inappropriate to make the final decisions based on appraisals as they are politically affiliated and are inclined to do their party's political bidding rather than base decisions on the recommendations of the HTA agency:

There should be a national coordinating board or commission that will be headed by a retired public official, and definitely not a minister for health. It should be someone

who is no longer in the political arena and doesn't have any stake in it. And who will not try to promote their political agenda. (Participant 23)

Lastly, another issue identified by participants to foster HTA establishment was the conduct and focus of the appraisal process. As much as participants considered HTA to be relevant for making decisions in the health system, they suggested consideration of factors other than economic and clinical evidence. Such factors include whose values would be reflected in the final decisions made, selection of topics, transparency and involvement of stakeholders:

When we have various options, and we need to choose from, we need to be very cognisant of the ethics; ethics must come in properly. Who is deciding what? The people who are deciding to use for instance drug A or B, are they making their personal values impact on their decision? So who will decide ultimately and will their values affect what we are talking about, ultimately, we have to establish that. (Participant 3)

....we should consider the ethics and the acceptability to the most of the people, this should be our priorities before we even start even thinking of money and cost. (Participant 1)

Also, under the appraisal process, some participants indicated the need to establish inclusion of factors such as societal values and ethics important in Ghanaian society for consideration. They were of the view that these will not have been captured by the economic evaluation study but was important for decisions affecting health delivery. Societal values were regarded as a contributing factor to the acceptance of policies, which included findings from HTA by users and the populace:

The orientation of the people is even different, and if you are going to do anything, it should revolve around that thinking, and that is why the societal values become very important. In Ghana, I think we need to bring our anthropologist and sociologist on

board to help in determining the societal values. It should not be one size fits all; it shouldn't be cascaded to fit every setting. (Participant 10)

These findings infer that participants were of the view that HTA can be introduced and used as intended if careful planning goes into its establishment. They called it 'preparation for HTA' and it included involving stakeholders in the preparatory process and formulating a legal and policy framework to mandate HTA use. They also suggested that the policy framework stipulate who conducts the appraisal, where that team is accommodated and other factors to consider in the final decision-making process in addition to the economic evidence presented. The next section presents participants' contributions on how HTA use could be promoted to ensure its success.

Promoting the use and success of HTA

Participants interpreted this theme as the factors that could be put in place to ensure that findings from HTA are used and their intended benefit achieved. Most participants indicated the need to foster the use and success of HTA after its successful establishment and initial use for decision-making in the Ghanaian health system. In line with this, they recommended education on HTA and the dissemination of information.

In terms of education, a majority of participants suggested continuous education of HTA users and stakeholders on HTA as an important way of promoting the use of recommendations from HTA appraisals. Participants interpreted education as, for example, formal training sessions to increase understanding of the HTA approach and its benefits to the health system. They suggested education of stakeholders as a precursor for use and success of HTA appraisals s in Ghana:

So at least everybody in the health sector needs to have some idea, I mean some cursory knowledge about health technology assessment: as a way of ensuring value for money

and prioritising intervention. So at least once we all have that common understanding, then when we are having discussions on plans and budgets for the year, we can understand why some decisions are made. (Participant 8)

…. it's just ignorance that will create a problem, but once you educate them as to exactly what health technology assessment is, why it's important in their area of work and those kind of things, and they see that it works, most people will not have problems with it. They will just accept and use it. (Participant 15)

In addition to education, most participants also recommended the dissemination of information concerning all aspects of HTA to promote and sustain the use and successes of HTA. This issue was of particular concern to participants at the district level of decision-making and those at national levels who saw themselves as not directly involved in formulating policies: NHIS and GHS. Dissemination of information was expressed as distributing findings of HTA, giving feedback on the implementation of findings of HTA and sharing experiences and successes to all users and appropriate stakeholders.

Sharing experiences and achievements in health outcomes was particularly perceived by a small number of participants as another means of getting those who may not be as receptive to support and use HTA:

I think documentation too is important. Sometimes we do things, and we don't document. As a Ministry, for instance, GNDP [Ghana National Drug Program] is doing all these good things, we should be able to document to say that we have a baseline of so much and because we took advantage of health technology assessment, we've been able to reduce our infant mortality rate from a certain figure to a lower figure. We have been able to decrease malnutrition from maybe 60% to 40%; we should

be able to document. Then once this documentary evidence is available it will even encourage others to get involved. (Participant 13)

From the results discussed above, participants are of the view that continually educating users of HTA, disseminating HTA reports and demonstrating impacts on the health system at all levels to stakeholders are ways in which its use could be promoted and intended benefit realised.

4.3.4 Conclusion

In summary, Ghanaian decision makers consider a range of factors in making decisions. They are however open to other ways of making decisions that utilise efficiency considerations. To summarise the identified barriers to the implementation and use of HTA and how they could be mitigated, one participant concluded the interview by stating:

I know that economic evaluation and HTA as such helps in priority setting. Because then you will know the intervention either the technical and allocating efficiency of whatever you are doing. The 'but' is still for me the politics and the capacity to do this on a wide range of interventions over the evidence. However, if we build capacity, and there is a change regarding advocacy for both the decision makers and politicians, then this will be a good way to set priorities in the health sector and in most of the policy reforms that we want to carry out. (Participant 21)

The next section presents discussion of findings of this study in relation to relevant literature.

4.4 Discussion

4.4.1 Current decision-making practices

Ghanaian decision makers consider an array of factors that may not necessarily be guided by written policy or guidelines when making decisions. Such factors include but are not limited to

those inherent in the health system (including guidelines (written and inferred), historical/past experiences and politics), and the perceived need and burden of the health system. These considerations are mostly framed by concern for the welfare of patients in terms of access to needed health services, and do not necessarily consider the health technology's effectiveness and cost effectiveness or the economic implications of decisions that are made. The factors mentioned above are similar to those considered by other decision makers, some of whom played different roles compared to the current participants, both in developing (5, 6) and developed countries (122, 124, 126, 127). Nonetheless, other decision makers in developed countries (126, 134, 151) reported they considered both economic and societal values such as benefits to the patient (126, 134).

Beyond the factors currently considered, participants recommended finding other efficient ways of making decisions that include not only the benefits to patients but also the costs, cost effectiveness and the financial impact of decisions on the entire health budget. This mirrors the recommendations of health managers in Argentina (130) and the UK (132) and researchers in Thailand (6).

Interestingly, when compared to the findings in Chapter 3, most of the factors that health workers perceived to be used by Ghanaian decision/policy makers were similar to those decision makers reported they used in the interviews. However, the decision makers interviewed did not report use of evidence of effectiveness and cost effectiveness of a health technology as decision-making criteria. It is worth noting that evidence of effectiveness and cost effectiveness were selected (through ranking) from the options provided in the questionnaire answered by clinical decision makers, unlike the national and district level decision makers who were asked open-ended questions in an in-depth interview.

The factors recommended for consideration in decision-making were also similar among clinical decision makers and decision makers. They include disease burden (needs assessment), population group and evidence of effectiveness. However, unlike national decision makers, those at the clinical facility levels and district health directors did not consider cost effectiveness and impact of health technology on overall health budget as an important benchmark to be taken into account in decision-making. However, although health workers reported that they were not satisfied with the overall decision-making process, they seemed to be satisfied with some of the factors considered for making decisions, similar to the decision makers.

The context in which decisions are made in the Ghanaian health system currently provides a good basis for the introduction of HTA into formal decision-making. This is because clinical decision makers perceived the current process as unfair, lacking transparency and leading to inappropriate use of public funds. On the other hand, national and district level decision makers discussed the need for a more efficient way of making decisions on the allocation of resources compared to the current system. Specifically, most of them were concerned that cost implications, effectiveness, cost effectiveness and the opportunity cost of a particular decision be taken into account.

Given the current state of the Ghanaian health system, where additional resources are not forthcoming (42), there are general concerns around what health resources are used for, whether they are appropriate and how allocation decisions are made. Also, in a context where politics is perceived as the main influence on major decision-making especially in resource allocation (47, 55), some participants (both researchers and decision makers) were open to a process they perceived as being more likely to ensure the efficient use of resources in a transparent way using scientific evidence. Consequently, participants demonstrated a positive attitude towards the use of HTA in the Ghanaian health system. Some perceived it as an

efficient and better way to ensure value for money and legitimacy for particular decisions. However, when asked about their knowledge of HTA, it was clear that this was limited among both researchers and decision makers.

4.4.2 Knowledge about and perceptions of HTA

Unlike clinical decision makers, more than half of the national and district level decision makers reported having some form of knowledge of economic evaluation. The findings are similar to those in other LMIC where a limited knowledge of EE was also reported (2, 5, 6, 18). However, the knowledge of HTA was very limited, and this presents as a major barrier to the use of HTA in Ghana. The lack of knowledge of HTA methods as a barrier has been identified in other developing countries (2, 6), whereas poor awareness of findings together with lack of knowledge of existence of such studies has been identified in high-income countries (31, 129, 133). Both qualitative (5, 6, 31, 127) and quantitative (2, 18, 123, 124) research has identified the lack of knowledge as a limitation to the use of HTA methods. The findings of this study tends to support this as perceptions of participants in this study about the meaning of HTA and its uses were diverse.

Participants had mixed suggestions when asked about the potential uses of HTA in the Ghanaian health system. These included setting standards for its conduct, cost containment, guidelines for the allocation of scarce resources and justification for resource use. The potential uses are comparable to those reported by some studies conducted in developing countries (2, 5, 6, 119, 130). It also corroborates the findings of Erntoft (151) in her review of the use of HTA methods by decision makers for pharmaceutical reimbursement decisions, where she identified that decision makers were likely to use HTA methods when they needed to provide reasons for requesting additional resources outside their regular budget.

4.4.3 Perceived barriers to HTA use

Although decision makers and researchers had a positive attitude towards the use of EE/HTA, they anticipated some barriers that could prevent adoption and use, and made some recommendations about how to overcome these. The barriers identified were lack of human capacity, data and financial resources, lack of knowledge and understanding about EE/HTA, political and media interference, competing interests, the historical way of making decisions and the vested interests of stakeholders.

Lack of resources

HTA is a resource intensive process requiring financial commitment, human resource capacity, and quality data that are adequate and readily available. Participants acknowledged the lack of financial, human and data resources as a barrier to the conduct and use of HTA in the health system which is comparable to that reported in studies of developing countries with similar characteristics in terms of the use of HTA methods (2, 5, 6, 18, 119, 120, 130). A study conducted in Canada, a high-income country, cited the lack of human, finance, data and time resources for the conduct of HTA as a limitation to the use of HTA at the local (hospital) level (125). Ghanaian decision makers and researchers, however, did not mention time as a barrier, unlike Canadian decision makers. This could be attributed to the fact that HTA is currently not being used, hence decision makers do not have any idea of how time-intensive it might be.

As reported in this study, limited availability of data has also been noted by decision makers and researchers as a potential and real barrier to the use of EE for decision-making in Latin America (5) and Thailand (6). Participants from these studies anticipated problems with the production and collation of quality data as potential barriers. Although some decision makers have also cited the lack of data as a barrier in settings where the use of EE for decision-making was already initiated, the data being referred to were the product of EE. Decision makers at the local level in the UK who were not using EE cited the limited and inaccessible nature of

evidence as their reasons (31). Also, the medicine management committee in two hospitals in North England indicated that the limited availability of EE studies concerning the technologies under consideration was a barrier to its use (131).

Insufficient funds for HTA specific activities has been reported as a barrier in both developed (125) and developing countries (2, 5, 6, 18), with Ghana being no exception. Thus, it can be concluded that funding remains an important barrier to the conduct and use of HTA methods irrespective of the income level of the country, especially during its introductory phase.

Politico-cultural barriers

Unlike the studies conducted in Thailand and Latin America (2, 5, 6, 119, 120, 130), and those conducted in high-income countries (122-124, 129, 131-133), distrust in the methodological approaches to economic evaluation were not indicated by Ghanaian decision makers as a major barrier to its potential use. These differences may be because most of the participants did not have in-depth knowledge of HTA. In addition, in Ghana, there is a general acceptance of anything recommended for use by the international community (for example, by WHO) as being of good quality. Therefore, with participants' prior trust in HTA as a 'good approach' for decision-making, the barriers identified were restricted to its production, acceptance, and effective use.

Political influence on decision-making in the health system was considered by participants of this study as a major potential hindrance to HTA use, just as reported in other developing countries' health systems (2, 4-6, 152). The influence of politics in decision-making is also reported in some high-income countries. For example, in the United States the use of cost effectiveness for funding new technologies under Medicare was abandoned due to political opposition. Also, the Oregon Medicaid cost effectiveness ranking of services was abandoned for political reasons (153).

Harris et al. (154) point to the influence of politics in the Australian health system in their analyses of the factors that impact reimbursement decisions for pharmaceuticals. This occurs particularly in cases where funding is requested for health technologies used in the treatment of life-threatening conditions. In other instances, political factors were observed generally as a response to lobby groups or personal interest.

In addition, while some decision makers in the present study perceived pharmaceutical companies to be resistant to the introduction of HTA because of their opinion that companies would benefit more in the absence of policies managing the approval of drugs and their reimbursement (such as the use of economic evidence), previous research reports a different perspective (123, 124, 131). They reported that decision makers were not likely to use HTA methods because they perceived pharmaceutical companies as sponsors of HTA methods such as EE, thus results were liable to be in their favour.

Furthermore, participants acknowledged that there were competing interests for health resources and that monies spent on HTA, which was perceived as expensive, could be spent elsewhere. Thus, they were concerned about the monies that would be allocated for HTA appraisals and not the effect of implementing HTA results on the health budget. Drummond et al. (123) in the UK reported that decision makers were more concerned about what implementing the findings of HTA methods meant to their decisions regarding resource allocation. These decision makers were unlikely to implement findings from HTA methods if it meant disinvestment in another technology or reallocating resources in a way which did not align with their short term goals.

Lastly, participants in this study perceived the historical way of making decisions in the health system as a potential major barrier to the use of HTA, as also reported by some Thai policy makers (6). A habituated process of making decisions can lead to resistance to a new way of

making decisions in the health system. Therefore, understanding the interests and needs of stakeholders in the health system is the first step in encouraging them to embrace a new method of decision-making. Lessons can be learnt from the experiences of other countries such as the UK and Australia where studies conducted in the early years of HTA institutionalisation reported that evidence from EE and HTA studies were in limited use by local decision makers because of institutional barriers, professional value systems and perceived benefits (31, 126), even though the information was accessible.

The politico-cultural barriers identified by participants are in line with Weiss' interactive model of decision-making which suggests that decisions are made considering not only the evidence available, but more importantly, other factors such as balancing competing interests and making compromises (155). Some factors interact during policy decision-making, therefore, identifying and addressing them can facilitate the introduction and use of HTA in the Ghanaian health system.

4.4.4 Recommendations to overcome perceived barriers and foster HTA use

The recommendations made by participants to address the stated barriers were establishing an HTA agency and promoting the use and success of HTA. They recommended measures to develop human capacity, collect and manage the needed data and the provision of sufficient funds to undertake HTA activities. Also identified was the need to involve relevant stakeholders in the development of an HTA policy, and that the policy should stipulate the siting of the agency, composition of appraisal team, focus of the appraisals and ensuring that relevant stakeholders be involved in HTA processes. Lastly, to promote the use and success of HTA, participants suggested the dissemination of its findings and the continuous education of HTA users and stakeholders.

The resources (human, data and financial) suggested by participants as essential for HTA establishment constitute basic requirements, without which it cannot be adopted. These recommendations are similar to those reported in studies in Thailand (2, 6), Asia (18) and Latin America (5, 119, 130) that identified human capacity development, funding and investment in the required data management as preconditions for the successful implementation of HTA.

In another study conducted on developing countries, Chalkidou, Levine and Dillion (4) suggested the development of local technical capacity as a requirement for low and middle-income countries in making decisions that are locally informed (when using HTA methods). They also suggested local researchers collaborate with those from elsewhere with the requisite skills to develop local capacity, which is similar to that recommended by participants in this study. In addition, decision makers interviewed by Hivon et al. (125) in Canada cited the need to overcome the barrier of lack of resources (including human and financial) to promote the use of HTA. That said, a peculiar difference between developing and developed countries is that participants from the latter also recommended improving the methods used in synthesising available data to produce findings instead of making data and other resources available (32, 127, 129, 133).

Countries such as Thailand, UK, and Australia that have successfully used HTA to inform decision-making have laws and policies governing its operations. The use of HTA for decision-making is also reported as being systematic in settings where a national reimbursement agency uses economic evidence as one of the criteria to make such decisions (151). It is, therefore, not surprising that participants in this study recommended the development of an HTA policy framework to guide its conduct and implementation. In line with this, the new medicines policy makes provision for the establishment and use of HTA for decision-making in the Ghanaian health system (38).

The results of the current study emphasise the importance of stakeholder involvement in the appraisal process. This is similar to recommendations made by decision makers from other settings (122, 127). There is also evidence that the use and impact of HTA increases in settings where policy makers were involved in the research or had commissioned that research themselves (138, 156).

To encourage the use of findings and recommendations from HTA, interviewees suggested the continuous education of users, similar to other studies in both contexts where HTA is institutionalised and where it is not (2, 6, 30, 31, 131). Participants of this study were of the view that dissemination of HTA findings be facilitated as a way of promoting its use. These views are similar to the findings of Kolasa et al. (157) who recommended appropriate and effective communication of HTA findings to users.

Lastly, there is a direct relationship between all the suggested measures of overcoming barriers indicated (such human and data resource, stakeholder education and the setting up and conduct of HTA) and availability and commitment of funding. Therefore, to be able to establish and conduct HTA as a formal decision-making process, recurrent funding would need to be allocated for that purpose. As indicated by participants of the study, without a formal financial commitment to HTA, its use can never become a reality. The availability of funds to conduct HTA methods has similarly been reported in other studies as necessary to promote its use (6, 125, 137).

4.4.5 Limitations of this study

The use of a qualitative approach enabled this study to explore the study objectives and research questions in detail, however, some limitations of the study need to be mentioned.

First, the findings presented are the views of a small proportion of all Ghanaian decision makers and may not necessarily reflect the perceptions of all. However, to address this, the sampling

techniques used ensured that participants were from different health institutions, operated at different levels of decision-making and had different roles. The sample was selected to be representative of all Ghanaian health system decision makers. Saturation was reached before discontinuing interviews.

Second, there was no representative from the regional level therefore some decision-making practices specific to the regional level decision makers may have been missed, if they exist, and subsequently their perceived knowledge and attitude towards the use of HTA for decision-making is missing. However, the decision makers interviewed were involved in most of the important allocation decisions in the health system, hence, it is assumed that non-participation of regional level decision makers did not influence the results.

Finally, it is possible that my presence could have affected the responses of participants by stimulating them to respond according to what they thought was expected of them as decision makers or researchers. In addition, how the questions were phrased and how concepts that arose during the interviews were interpreted could have varied from participant to participant. To minimise this effect, an interview guide was used and care was taken not to deviate from it. It is, however, worth noting that based on the responses of interviewees, follow-up questions were asked on case-by-case basis.

4.5 Conclusion

This chapter provides useful information for the setting up of an HTA agency and development of an appraisal process that will be embraced and used by all stakeholders, if the country decides to implement the HTA approach. The decision-making practices of national decision makers in Ghana and their knowledge and perception about HTA has been presented. Currently, Ghanaian decision makers consider certain factors for making decisions such as patient and population welfare and health outcomes, but are open to other criteria that take the

economic implications of decisions into account. All categories of decision makers surveyed (health workers and national and local decision makers) were aware of a lack of transparency in the decision-making processes and the consequent inappropriate use of public funds. These concerns create an opportunity for the formal introduction of HTA for decision-making in this setting. When undertaken appropriately, HTA will address the concerns (which include consideration of economic evidence and lack of transparency in the current decision-making process) raised by all categories of decision makers as well as researchers.

In addition, one thing that was clear was the fact that Ghanaian decision makers follow directives from international bodies such as the WHO to design policies and make decisions for the Ghanaian health system. Therefore, with the global move towards using evidence for making decisions through for instance HTA, there is a good chance that Ghana will adopt and use HTA. That said, the important question that needs answering is whether Ghana is able to conduct and use HTA now?

This question must be addressed because, among other reasons/barriers, the findings reported in this chapter indicate that there is a paucity of knowledge of HTA among decision makers and researchers. It is therefore important that Ghana address these anticipated barriers to maximise the chances that, when introduced, the expected benefits to the health system of HTA will be realised. Some of the measures Ghana can put in place to address these barriers include: allocation of funds for HTA, education of stakeholders on HTA, involvement of stakeholders in the planning and introduction of HTA for decision-making, collation and management of data for HTA, training of people to be able to conduct HTA and relying on experts from other countries for HTA where possible. To begin this process, it is important that Ghana first examine the availability of the basic but necessary requirements needed to be able to conduct HTA: human, financial and data resources. This issue is explored separately in the next chapter, with the exception of financial resource availability, which is beyond the scope of this study.

5 HTA IN GHANA: CURRENT TECHNICAL CAPACITY

5.1 Introduction

This Chapter investigates the human and data (technical) capacity of Ghana to conduct HTA, which was recognised as a main barrier to HTA use for decision-making in the Ghanaian health system, as reported in Chapter 4. As noted in Chapter 2, economic evaluation studies form the bedrock of HTA, thus a review of published economic evaluations are used to provide information on the technical capacity of Ghana to conduct HTA. The review examines the quantity and quality of economic evaluation studies in Ghana, in particular, what studies are available for use in a HTA and for priority setting, including decisions regarding resource allocation. The number of local persons available to conduct and train people to conduct economic evaluation are also investigated. Specifically, this chapter:

1. Assessed the scope and quantity of studies.

   The objective was to identify the number of EE studies available for use in future HTA appraisals as well as the scope of technologies appraised and the conditions evaluated.

2. Assessed the quality of studies.

   The quality was assessed using a quality assessment tool to examine how studies are conducted and reported; and the usefulness of such studies for HTA appraisal.

3. Assessed if evidence from economic evaluations could be used for decision-making

   This was to investigate the usefulness of the existing economic evaluation studies on their own in the absence of a formal HTA appraisal process for decision-making.

4. Determined the labour and data capacity available

   The labour capacity was assessed by identifying the number of Ghanaian authors of HTA (including economic evaluation) studies based in Ghana. This was done to provide information on the supply (both current and future) of economic evaluation studies in

terms of capacity to conduct these and train people to do the evaluations. In addition, the review sought to identify the kind of data available and sources of cost and epidemiological data used in these studies for future use in similar studies.

This chapter is organised in five sections. Sections two, three and four present the methodological approach, results and interpretation of findings. The sub-sections under sections three and four are organised according to the objectives this chapter. Limitations of the review are also acknowledged under the discussion section. The major findings from the chapter are summarised with their implications on policy and research in the concluding section.

5.2 Methods

A systematic review of economic evaluations in Ghana was conducted. The aim of the review was to evaluate the quantity and quality of all economic evaluation studies available and provide a data synthesis[18]. Therefore, all the studies that fulfilled the predefined inclusion criteria were selected for the review.

5.2.1 Literature search

Inclusion criteria

Studies that met all the criteria outlined below were included in the review:

1. Health economic evaluation studies conducted in Ghana only and in Ghana along with other countries
2. Full economic evaluation studies (cost utility, cost effectiveness and cost benefit analysis) on both single health technologies and public health programs
3. Publication (peer-reviewed, reports, and working papers) with full article accessible

[18] A traditional systematic review seeks to synthesise data from different studies on a particular subject to ascertain a pooled estimate of effect and/or qualitatively a phenomenon. With this in mind, care is taken not to include studies of poor quality (158, 159), hence the use of a quality control guidelines/checklist to eliminate studies with flaws from the data synthesis. Data synthesis thus includes only studies that satisfied the quality control checklist.

4. Publication in English language

Exclusion criteria

Studies that met any of the following criteria were excluded from the review:

1. Studies that are not economic evaluations
2. Cost of illness studies
3. Economic evaluation studies not pertaining to health technologies
4. Grey literature

Search strategy

An initial full literature search was carried out in October 2015 and updated on November 2018 to identify economic evaluation studies conducted in Ghana from 1990 to 2018. The search was conducted in three electronic databases: Embase (including Ovid MEDLINE, Old Ovid MEDLINE and Ovid in process and other non-indexed citation), PUBMED and Google scholar. A manual search was carried out in the reference lists of included studies. The keywords used for the search included “cost effectiveness analysis”, “cost benefit analysis”, “cost utility analysis”, “costs and cost analysis”, “economics”, “health care costs”, “Ghana”, “economic value of life”, “economic evaluation”, “health technology assessment” and “technology assessment” in the title or abstract of articles.

5.2.2 Review process

The study used the PRISMA review guidelines and diagram (159) to guide the process of identifying papers relevant for the review.

Figure 5-1 illustrates the review process. After initial screening of 1116 papers, twenty-four (n=40) abstracts were selected for further review. The 1076 papers excluded were newsletters (n=17), cost of illness studies (n=55), WHO reports and software (n=5), economic evaluation studies but not in healthcare and/or about health technologies (n=3) and other studies conducted in Ghana but not economic evaluation (n=996). Out of the 40 abstracts reviewed in detail, fourteen (n=6) were excluded: five (n=11) were conference abstracts (full texts could not be located) one (n=1) was a brief commentary on a paper and the remaining (n=1) a thesis. Twenty-six (n=26) papers were included for review after final screening and extraction of full text articles.

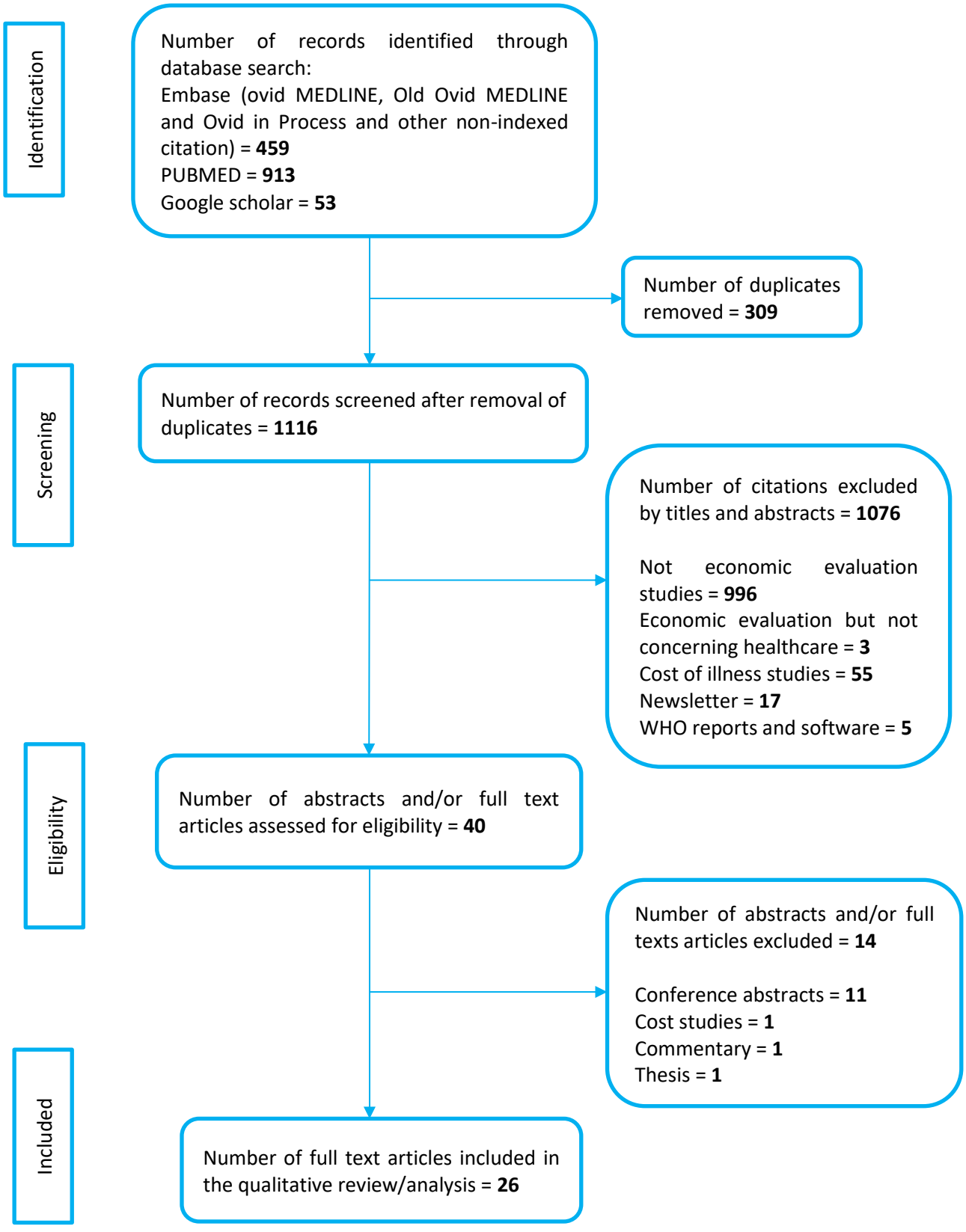

Identification
Number of records identified through database search:
Embase (ovid MEDLINE, Old Ovid MEDLINE and Ovid in Process and other non-indexed citation) = 459
PUBMED = 913
Google scholar = 53
Number of duplicates removed = 309
Screening
Number of records screened after removal of duplicates = 1116
Number of citations excluded by titles and abstracts = 1076
Not economic evaluation studies = 996
Economic evaluation but not concerning healthcare = 3
Cost of illness studies = 55
Newsletter = 17
WHO reports and software = 5
Eligibility
Number of abstracts and/or full text articles assessed for eligibility = 40
Number of abstracts and/or full texts articles excluded = 14
Conference abstracts = 11
Cost studies = 1
Commentary = 1
Thesis = 1
Included
Number of full text articles included in the qualitative review/analysis = 26

Figure 5-1: PRISMA chart illustrating the different phases of the systematic review

5.2.3 Data extraction and analysis

One person (the PhD candidate) did data extraction. The general and methodological characteristics were extracted using a standardised annotated form developed by the reviewer based on the Consolidated Health Economics Evaluation Reporting Standards (CHEERS) checklist, objectives of the review and literature reviewed on the quality of a health economic evaluation studies. The general characteristics extracted include year of publication, nationality/origin of lead/corresponding author, journal of publication, type of disease/condition being evaluated, category of care, source of funding, type of technology evaluated and the use of a model for evaluation.

The methodological characteristics extracted were type of economic analysis, perspective of analysis, type of model used, costs included, health outcome measure, source of data and type of sensitivity analysis. The articles were reviewed and the data extracted twice by the same reviewer at two different periods (five months apart) to minimise inaccuracies and misinterpretations as much as possible. Discrepancies between the data extracted from a single study at the different time points were investigated and reconciled. Data were entered and analysed in Microsoft Excel 2015. Descriptive statistical analysis including percentages and frequencies were used to describe the characteristics of the studies. Tables and figures such as bar and column charts were also used to present the results.

The findings from this chapter were compared to similar studies conducted in developing countries only. This is because it was assumed that these countries have similar characteristics to Ghana in terms of their capacity to conduct HTA. In addition, similar to Ghana, at the time that those studies were conducted, the use of HTA methods were not formally required as a decision-making criterion in these settings.

Scope and quantity of studies

The quantity of economic evaluation studies available in Ghana was determined through the number of studies identified that satisfied the inclusion criteria. The scope of studies was determined by examining the conditions that were evaluated by the studies. These were categorised as communicable and non-communicable diseases.

Quality assessment of studies

The quality of HTA is dependent on the quality of economic evaluation studies that are in turn reliant on the methodological approach used and subsequent reporting. To ensure quality of economic evaluations, a number of countries and organisations have adopted the use of guidelines for conducting and reporting EE studies. Such guidelines include the WHO guidelines for cost effectiveness analysis (93), the Gates reference case of the Bill and Melinda Gates Foundation (95), the iDSi reference case for EE (96) and the CHEERS by the ISPOR (160).

Currently, there are no existing guidelines for the conduct of EE studies developed or adopted for use in Ghana. Therefore, in reviewing the quality of EE studies published with Ghana as a study setting, the CHEERS checklist was chosen by this study because of, among other reasons,

its comprehensiveness, and because currently most international journals on health economics recommend its use for reporting economic evaluation studies [19].

The CHEERS checklist comprises six main categories with 24 criteria (see Appendix 4 Table 11-10 for the checklist). Category 1 examines the title and abstract and covers questions 1-2. Category 2 looks at the introduction to ascertain if it captures the broader context of the study, and covers question 3. Category 3 queries the methodological approach to the study for appropriateness and consists of general methodological issues such as perspective of study as well as outcome measures used. Questions 4-17 relate to the methods category.

Category 4 further examines the results section for comprehensiveness and transparency of reporting findings of studies, and covers questions 18-21. Category 5 entails the discussion of results amidst current knowledge and limitations of studies and is addressed by question 22. Category 6 examines other characteristics such as declaration of funding and conflict of interest in questions 23-24 (160). Each criterion is answered using 'yes' or 'no', hence the quality score of the study is estimated by counting the number of 'yes' incidences. Thus, for the purposes of this study, the higher the count, the higher the quality of the study assessed. A perfect quality score for a study using CHEERS checklist is 24: the higher the score, the better the quality of the study and vice versa.

For this review, criterion 12 of the CHEERS checklist (whether the source of the QALYs weights used was stated and whether the method was stated explicitly) was assessed by checking if the study described how DALYs or QALYs were estimated. This modification was introduced because unlike studies from high-income countries, which typically use QALYs,

[19] Although the checklist was not developed for the purposes of assessing the quality of EE studies, its aim was to ensure good and quality conduct and reporting of such studies. Therefore, this study uses it as a quality assessment tool. Other checklists/instruments that exist for reporting economic evaluation studies as well as assessing their quality include the Quality of Health Economics Study (QHES) instrument (161), Drummond et al.'s checklist for assessing economic evaluation studies (8) (which has now been replaced by CHEERS checklist) and the Consensus on Health Economic Criteria (CHEC) checklist (162).

those conducted in developing countries often use DALYs as a measure of health outcome. This is because (among other reasons such as its recognition by donor partners and funding agencies such as the World Bank), patient/population preference-based studies used to derive utility weights for the estimation of QALYs are not usually undertaken in developing countries. Thus, a study was accorded 'yes' for criterion 12 if it either used DALYs or QALYs as the measure of health outcome and described how these were estimated.

Determining if evidence from economic evaluations is useful on its own

This study did a comparative analysis of studies evaluating the same health condition to investigate if a decision maker could make a choice among these based on the characteristics and findings reported.

Labour and data capacity for HTA

The number of local persons who authored the studies reviewed were used as a proxy to determine the local capacity available for HTA. The data capacity was assessed by evaluating the type and sources of data (covered under the methods section of the CHEERS checklist) used by each study.

5.3 Results

5.3.1 Study characteristics

Twenty-six (n=26) studies were included in the review. Of these, 15 were CUA with the remaining 11 being CEA. Fifteen (96%) of the papers reviewed were published between 2000 and 2018; 80% of these were published after 2010. Figure 5-2 gives a detailed distribution of the years in which papers were published. All the studies were published in international journals, even though there are local journals available.

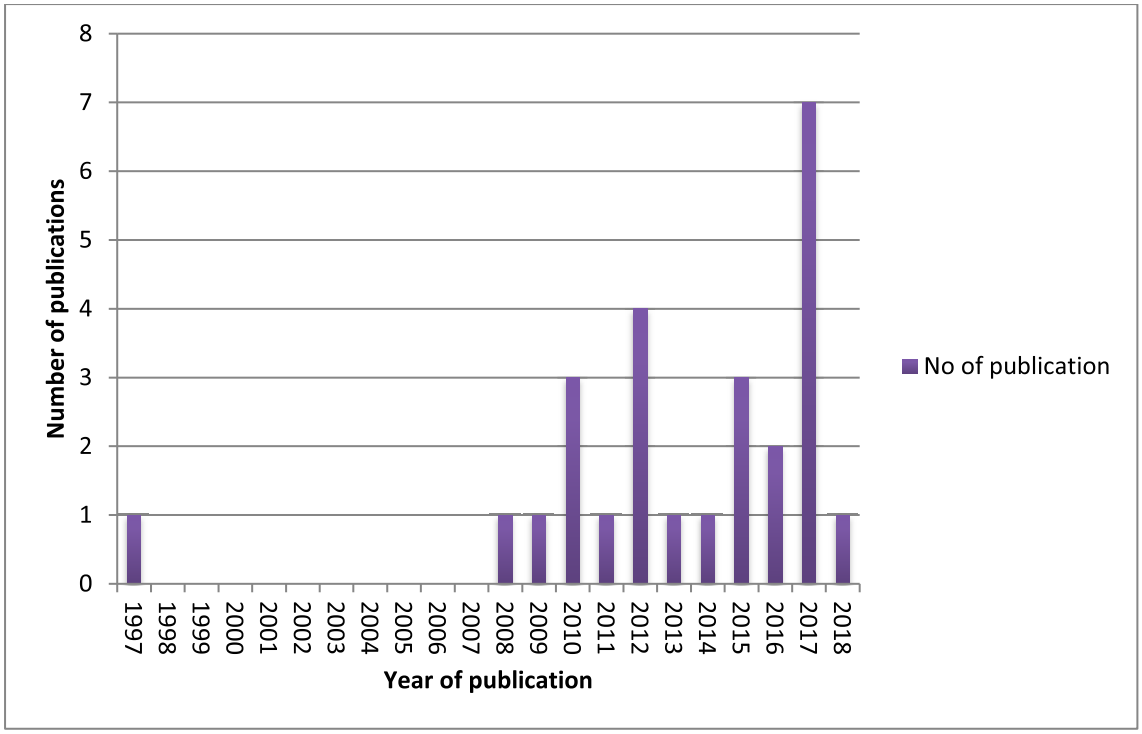


Figure 5-2: Distribution of publications per year

Twenty-one of the 26 studies were conducted in the Ghanaian setting only. The remaining five were studies in a number of countries, including Ghana (163-165). Fourteen (n=14) studies (163-172) used a model to evaluate the health technology being appraised; the remaining 12 (173-180) did not specify the use of a model. Some important characteristics of studies reviewed are described in Table 5-1.

Table 5-1: Characteristics of economic evaluation studies in Ghana

Study	Perspective of analysis	Source of data	Time horizon	Type of economic evaluation	Disease/Condition	Technology being evaluated	Type of model
Binka, Mensah and Mills (1997)	Not specified	Clinical trial	2 years	CEA	Malaria	Permethrin impregnated mosquito net	Not specified
van Hulst et al. (2008)	Societal	Local facility data and published literature	Lifetime	CUA	HIV	HIV screening	Decision tree and Markov
van Hulst et al. (2009)	Health provider	Hospital data and published literature	< 1 year	CUA	HIV and all forms of hepatitis	Blood screening	Markov
Schillcutt et al. (2010)	Provider and patient	Program and published literature	Not specified	CUA	Hernia	Surgical intervention	Not specified
Hu et al. (2010)	Health payer and societal	Local hospital data and published literature	Not specified	CEA	Abortions	Treatment intervention	Markov
Conteh et al. (2010)	Public provider and societal	Clinical trial	18 months	CEA	Malaria	Antimalarials (malaria prophylaxis)	Not specified
Witternborn and Rein (2011)	Societal	Published literature	Lifetime	CUA	Glaucoma	Glaucoma interventions	Validated glaucoma
Nonvignon et al. (2012)	Societal	Clinical trial	4 years	CUA	Malaria	Antimalarials	Not specified
Abotsi et al. (2012)	Provider	Ongoing program	2 years	CEA	Malaria	Antimalarials (malaria prophylaxis)	Not specified
Abbott et al. (2012)	Provider	Clinical trial and published literature	5 years	CUA	Childhood diarrhoea diseases	Rotavirus vaccine	Yes (but not specified)
Zelle et al. (2012)	Healthcare provider	Published literature and local data	10 years	CUA	Breast cancer	Breast cancer control	Yes (but not specified)
Ansah et al. (2013)	Provider and societal	Clinical trial	1 year	CEA	Malaria	Rapid diagnostic test	Decision tree
Paintain et al. (2014)	Provider and societal	Before and after design	1 year	CEA	Malaria	Mosquito net	Basic economic
VanDeusen et al. (2015)	Not specified	Local hospital data and published literature	Lifetime	CUA	HIV	Option B plus medicine	Decision tree and Markov
Dalaba et al. (2015)	Provider	Before and after design	1 year	CEA	Maternal health	Medical intervention	Not specified
Pitt et al. (2016)	Public provider	Clinical trial	1 year	CEA	Child health	Home visits	Decision tree

Study	Perspective of analysis	Source of data	Time horizon	Type of economic evaluation	Disease/Condition	Technology being evaluated	Type of model
Nonvignon et al. (2016)	Provider and societal	Program and other published literature	< 1 year	CEA	Malaria	Antimalarials (malaria prophylaxis)	Not specified
Tawiah et al. (2016)	Health sector and societal	Clinical trials and survey for household cost	2 years	CEA	Malaria	Rapid diagnostic test	Decision tree
Escribano et al. (2017)	Societal	Survey and published data	Not specified	CEA	Childhood malaria, diarrhoea and pneumonia	Treatment programs: ICCM and CHPS	Not specified
Goodman et al. (2017)	Not specified	Program and local data on wages	5 years	CUA	Maternal and child health	Quality improvement program	Not specified
Gyedu et al. (2017)	Not specified	Program	Not specified	CUA	Surgeries	Outreach program	Not specified
Nonvignon et al. (2017)	Health system and societal	Published literature	5/20 years	CUA	Childhood diarrhoea	Rotavirus vaccine	Decision analytic
Russel et al. (2017)	Not specified	Published literature	Lifetime	CUA	Neonatal health	Group B streptococcus vaccine	Decision tree and Markov
Wilcox et al. (2017)	Provider	Program and published literature	3 years	CUA	Maternal and child health	Program: basic emergency obstetric and newborn care	Decision tree
Basu, Shankar and Yudnik (2017)	Societal	Published literature	Lifetime	CUA	Diabetes	Diabetes treatment	Microsimulation
Asamani 2018	Health system	Clinical trial and other published literature	Lifetime	CUA	Chronic heart failure	Drug: Entresto TM	Markov

Abbreviations: CEA: Cost effectiveness analysis, CUA: Cost utility analysis, DALY: Disability adjusted life years, LLIN: Long lasting insecticidal nets, QALYs: Quality adjusted life years, HIV: Human immunodeficiency virus.

Table 5-1 continued: Characteristics of economic evaluation studies in Ghana continued

Study	Costs included	Discount rate	Sensitivity analysis	Number of authors	Outcome/effectiveness measure	Source of funding
Binka, Mensah and Mills (1997)	Direct and indirect	3%	Univariate and multivariate	3	Child deaths averted, discounted life years gained	International
van Hulst et al. (2008)	Direct and indirect	3%	Probabilistic and univariate	11	DALYs averted (age weighting for base case)	International
van Hulst et al. (2009)	Direct only	3%	Univariate	9	DALYs averted (age weighting for base case)	International
Schillcutt et al. (2010)	Direct and indirect	3%	Probabilistic	3	DALYs averted	International
Hu et al. (2010)	Direct only	3%	Univariate and multivariate	6	Years of lives saved	International
Conteh et al. (2010)	Direct and indirect	3%	Probabilistic	6	Malaria episodes averted	International
Witternborn and Rein (2011)	Direct and indirect	3%	Univariate	2	DALYs gained	International
Nonvignon et al. (2012)	Direct and indirect	3%	Univariate and multivariate	7	DALYs saved/gained, anaemia cases averted, number of deaths due to malaria averted	International
Abotsi et al. (2012)	Direct and indirect	3%	Univariate	7	Malaria cases averted, number of deaths due to malaria averted, DALYs saved*	Self-funded
Abbott et al. (2012)	Direct only	3%	Univariate and multivariate	4	DALYs averted	International
Zelle et al. (2012)	Direct and indirect	3%	Univariate	9	DALYs averted	International
Ansah et al. (2013)	Direct and indirect	5%	Univariate and multivariate	5	Correctly treated fever	International
Paintain et al. (2014)	Direct and indirect	3%	Univariate	15	Additional number of persons using an LLIN, additional number of children under five years using an LLIN, additional number of all-cause under five deaths averted	International
VanDeusen et al. (2015)	Direct and indirect	3%	Univariate	4	QALYs gained, HIV infections averted among newborns	International
Dalaba et al. (2015)	Direct only	3%	Univariate	9	Detection of pregnancy complications, reduction in labour complications	International

Study	Costs included	Discount rate	Sensitivity analysis	Number of authors	Outcome/effectiveness measure	Source of funding
Pitt et al. (2016)	Direct and indirect	3%	Probabilistic and univariate	10	Years of lives saved (discounted), neonatal mortality averted	International
Nonvignon et al. (2016)	Direct and indirect	3%	Univariate	9	Additional number of malaria cases and deaths averted	International
Tawiah et al (2016)	Direct and indirect cost	5%	Probabilistic and univariate	10	Appropriate treatment of malaria with Artemeter Lumefantrine	International
Escribano et al. (2017)	Direct and indirect cost	3%	Univariate	12	Appropriate diagnosis and treatment given	International
Goodman et al. (2017)	Direct and indirect cost	Not specified	Univariate	8	DALYs	International
Gyedu et al. (2017)	Direct and indirect cost	Not specified	None	4	DALYs	International and local
Nonvignon et al. (2017)	Direct and indirect cost	3%	Univariate	8	DALYs	International
Russel et al. (2017)	Direct costs	3%	Probabilistic and univariate	8	DALYs	International
Wilcox et al. (2017)	Direct costs	3%	Probabilistic and univariate	6	DALYs	International
Basu, Shankar and Yudnik (2017)	Direct and indirect cost	3%	Univariate	3	DALYs	Not specified
Asamani 2018	Direct costs	3.5%	Probabilistic and univariate	1	QALYs	Not specified

Abbreviations: CEA: Cost effectiveness analysis; CUA: Cost utility analysis; DALYs: Disability adjusted life years; LLIN: Long lasting insecticidal nets; QALYs: Quality adjusted life years; HIV: Human immunodeficiency virus

Definitions: Direct costs are costs incurred by undertaking the program and/or using the technology. These includes cost of labour, technology, training, equipment and transportation. Indirect costs are costs that cannot be easily apportioned to the technology under evaluation. These include productivity loss due to illness, caregiving, volunteering and school days lost.

5.3.2 Scope and quantity of studies

The review identified 26 economic evaluations in Ghana for an HTA appraisal. Technologies evaluated were drugs (35%), treatment interventions (19%), diagnostics/screening (19%) and others including programs (27%). Of these technologies, 58% encompassed preventive care and the remaining curative care. The majority (58%) of the studies evaluated non-communicable diseases (Table 5-1). Eight papers covered various malaria interventions (167, 169, 173-175, 177-179); the remaining evaluated interventions for maternal and child health (166, 168, 176, 181-185), HIV infection (164, 170, 171), hepatitis B and C (164) (n=1), hernia (180), diabetes (186), chronic heart failure (187) glaucoma (165), abortion (163), breast cancer (172) and surgeries (188).

5.3.3 Quality of studies

Overall the mean quality score was 20.12 (SD 1.99) out of 24. The lowest score was 14 and that with highest score was 23. Surprisingly, the study with the lowest score was published in 2017 compared to the second lowest, which was the first to ever be conducted in Ghana and would be expected to have the least quality score[20]. The quality of studies (assumed as synonymous to the quality in their reporting) reviewed is described in detail according to the six main categories of the CHEERS checklist. Figure 5-3 illustrates the number of studies that satisfied each of the 24 quality criteria. Categories 1, 2, and 5 were well described. The remaining categories; 3, 4 and 6 were less well described, especially category 4 where the criterion that assesses the characterisation of heterogeneity was rarely addressed by studies. Table 5-2 also shows the quality assessment score of each study.

[20] As there has been development of methods and reporting standards of economic evaluation since the first study was published, the mean quality of all studies was re-assessed by omitting this study to investigate its impact on the overall quality of the economic evaluation studies reviewed. The mean quality score was 20.28 out of 24, which is not very different from 20.12. Hence, inclusion or exclusion of the first paper did not have much impact on the overall quality of economic evaluation studies in Ghana.

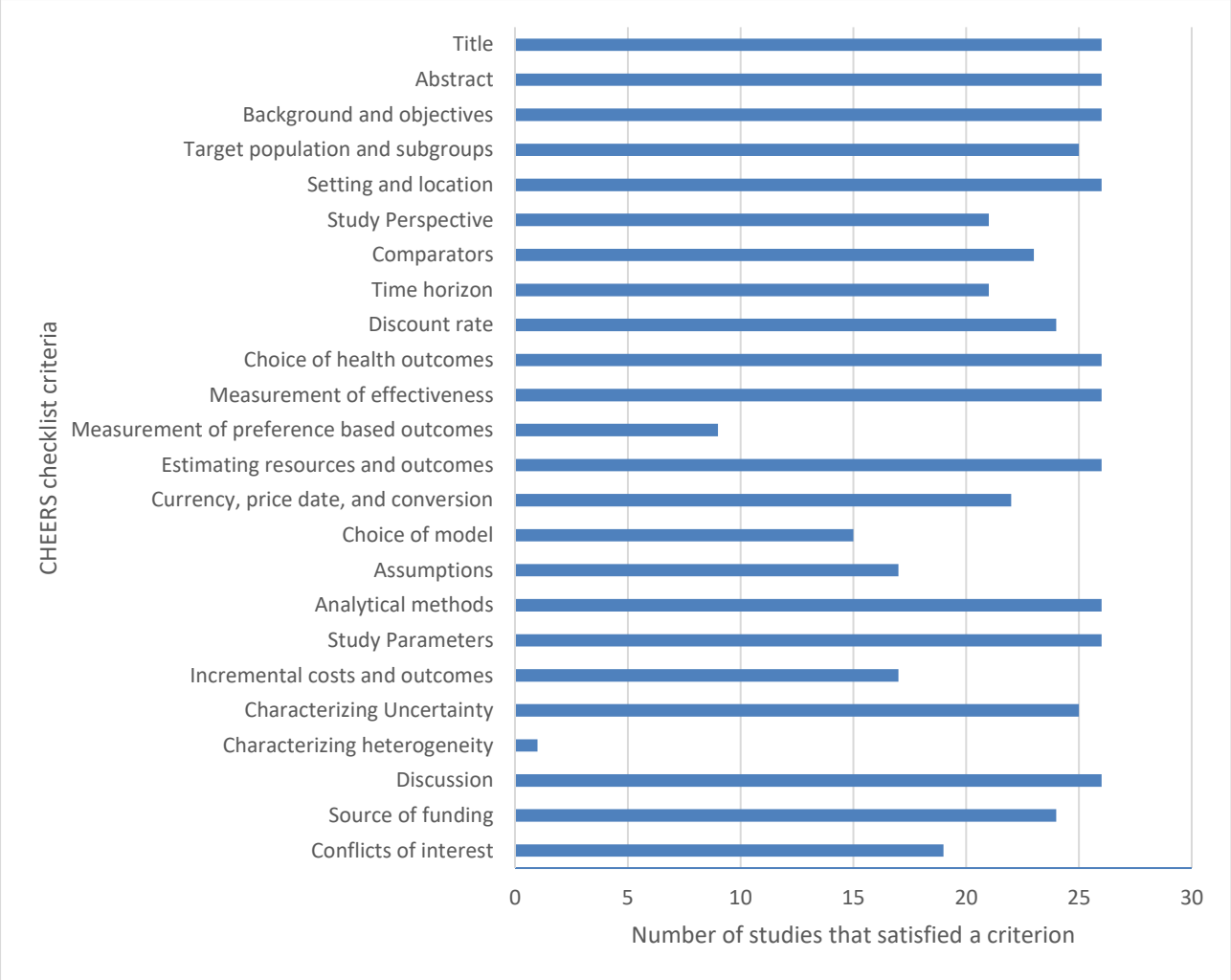
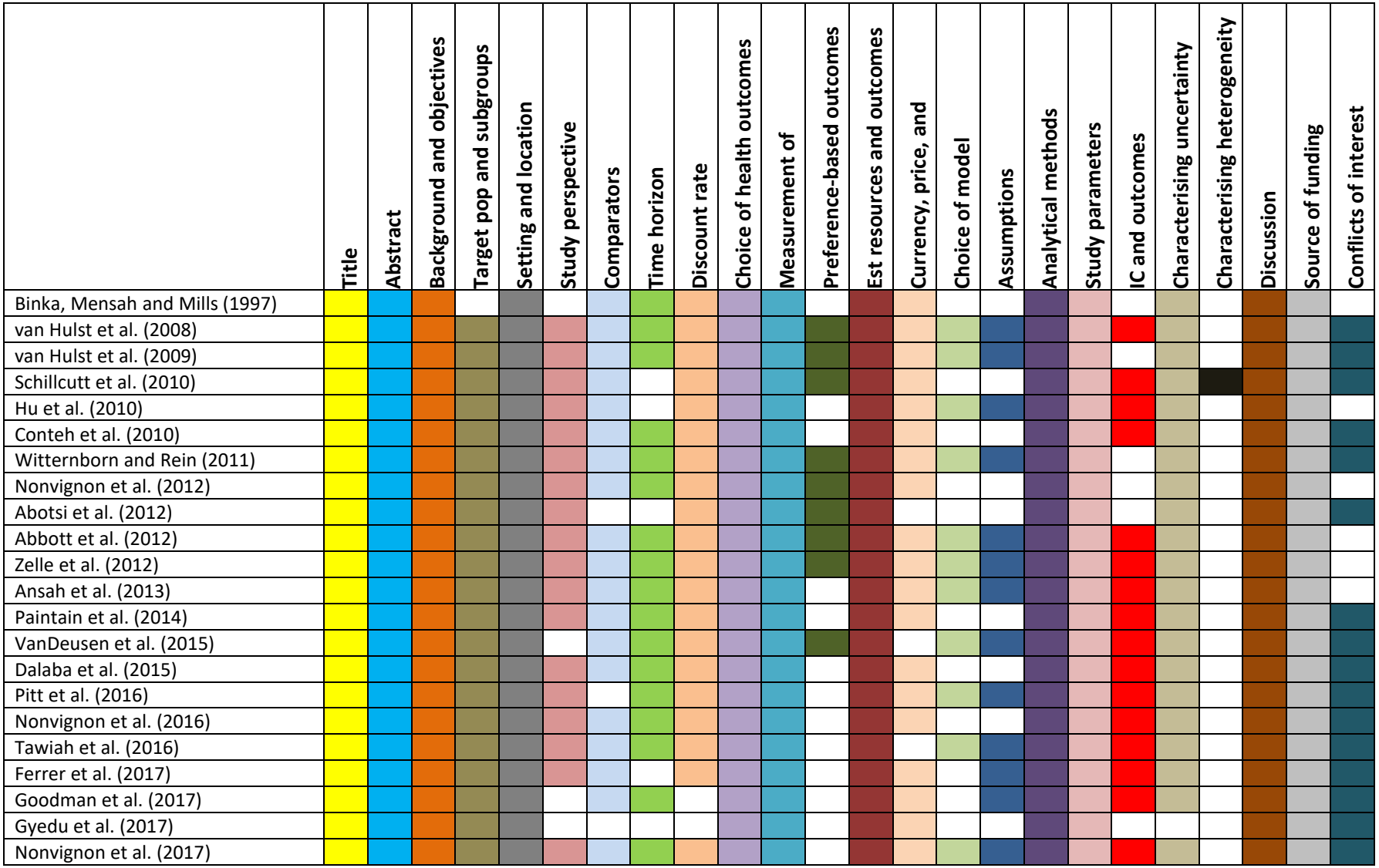


Figure 5-3: The number of studies that satisfied each criterion of the CHEERS checklist

Table 5-2: The quality scores of studies reviewed



	Title	Abstract	Background and objectives	Target pop and subgroups	Setting and location	Study perspective	Comparators	Time horizon	Discount rate	Choice of health outcomes	Measurement of	Preference-based outcomes	Est resources and outcomes	Currency, price, and	Choice of model	Assumptions	Analytical methods	Study parameters	IC and outcomes	Characterising uncertainty	Characterising heterogeneity	Discussion	Source of funding	Conflicts of interest
Russel et al. (2017)																								
Wilcox et al. (2017)																								
Basu, Shankar and Yudnik (2017)																								
Asamani 2018																								

Each column contains a keyword for each criterion (question) on the CHEERS checklist used for the quality review in the study. A colour coded cell signifies study satisfied the criterion and was assigned a 'yes', hence a count of one (1). A 'blank' (colourless/white) cell denotes that study did not satisfy the criterion hence was assigned a 'no', count of zero (0).

Abbreviations: Est: estimation, IC: incremental cost, pop: population.

Category 1: Title and abstract

The title of all 26 studies used specific terms that identified them as an economic evaluation study. All of the titles included the term 'cost effectiveness'. Their abstracts were comprehensive capturing the background, study objective, methods, results and conclusions, and were outlined in a structured manner for easy reading and understanding.

Category 2: Introduction

The introduction of all 26 studies provided the context in which the economic evaluation was conducted. The objectives and relevance of studies were outlined, providing the decision maker with sufficient information to guide appropriate decision-making.

Category 3: Methods

Of the 14 criteria that describe the methodological quality of studies, five (setting and location, choice of health outcomes, measurement of effectiveness, estimating resources and outcomes and analytical methods) were satisfied by all studies reviewed as shown in Figure 5-3. Only one study did not describe the target population and subgroups. The setting and location of all studies were comprehensively described. Although 21 studies stated the perspective from which the evaluation was conducted, only two (172, 175) gave reasons for their choice. The predominant perspective was provider/payer (n= 8), followed by provider and societal (n=7). Five studies also conducted their analysis from the societal perspective only.

Three studies failed to describe the alternative interventions under comparison. All the studies had a 'do nothing'/ 'null' as one of the counterfactual interventions. Twenty-one studies specified the time horizon used to estimate costs and consequences of interventions. This ranged from less than 1 year (n=2), between 1 and 5 years (n = 13), 6 – 10 years (n = 1) and lifetime (n = 6). All the studies except two discounted costs and health outcomes beyond one year. The most commonly used discount rate was 3% (used by 21 studies). Only two studies

(167, 169) used a discount rate of 5% and the remaining used 3.5% (187). The selection of discount rates was duly justified in these studies.

The choice of health outcomes whether measured in natural units or preference-based measures were explicitly stated in all studies. Eleven studies, which were all CEA, reported health outcomes in natural units only. DALYs only were used by 12 studies whilst one study used QALYs only. Three studies also reported both DALYs and natural units (173, 178) or QALYs and natural units (171). However, even though 16 studies used DALYs and QALYs, only nine studies (163-166, 171-173, 178, 180) out of the 16 described how they were measured. Years of lives saved and healthy life years gained were also the choice of health outcomes for some studies. These and other study characteristics are presented in Table 5-1. Subsequently, these studies described how effectiveness was measured.

Resource use and methods used to estimate costs and outcomes for alternative health interventions were described. Some studies stated the costing approach used (n=8), but the remaining failed to mention this although they listed the type of resources and costs measured and estimated. While some (n = 19) estimated both the direct and indirect costs[21] of interventions, others (n = 7) estimated only the direct costs. The cost analyses approach used by studies were micro costing (also known as ingredients costing), step down and bottom up. Only four studies (169, 171, 173, 186) failed to report the conversion rate used to report costs and how it was done. All studies reported costs in US dollars.

Fourteen studies specified the use of a model and described all the assumptions underpinning the model however six failed to present the structure of the model in the paper. The remaining studies that did not specify the use or non-use of a model had a local person as a lead author.

[21] Indirect costs are costs that are expended in the form of productivity loss due to cessation or reduction of work, in order to contribute to an intervention. They include volunteerism.

The sources of both cost and effectiveness data for the studies were of good quality and are described under the data capacity section (sub-section 5.3.5).

Category 4: Results

As presented in Figure 5-3, all 18 studies reported health outcome, resource use, and costs of resources. While some (n=4) reported the unit cost together with the total costs of all cost centres, others reported only the latter. Most of the studies that used 'do nothing' as the only comparator (n = 7) did not present the costs and outcomes for the two alternatives under evaluation in a table, though the consequences (used in estimating that of the intervention) were sometimes mentioned in their write-up. These studies reported the costs and outcomes of the interventions as the additional costs and outcomes, which were used to estimate the ICER. Seventeen studies estimated the incremental costs and outcomes of interventions under comparison. The remaining nine reported only the cost effectiveness ratio (CER) (the average cost of intervention), which is not sufficient for decision makers who require an incremental analysis about the additional cost per unit of benefit over current practice.

All the studies examined but one (188) characterised the parameter uncertainties to ascertain robustness through a sensitivity analysis. The most common sensitivity analysis conducted was univariate (46%). Eight (n=8) studies conducted a probabilistic sensitivity analysis while five (n=5) other studies conducted both univariate and multivariate sensitivity analysis. None of the studies assessed the structural uncertainty of the model used. Only one study (180) described the differences in costs and outcomes of patients with different characteristics and evaluated how that could contribute to variations in the cost effectiveness of the intervention between these subgroups.

Category 5: Discussion

The 26 studies assessed discussed their key findings in the context of current knowledge. The limitations as well as how the studies could be generalised in the country and other similar settings were addressed. The cost effectiveness and affordability of interventions were also addressed using the cost effectiveness threshold previously recommended for use by WHO and the World Bank (189). This compares ICER/CER to the per capita GDP of the country of study: the GDP per capita of a country as the cost effectiveness threshold. It states that any health technology with an ICER/CER less than the per capita GDP of a country is considered highly cost effective and one that is less than three times the per capita GDP of the country as cost effective. On the other hand, health technology with an ICER/CER of more than three times the per capita GDP of the country is not considered cost effective.

It is worth noting that currently the WHO has withdrawn this cost effectiveness threshold that has been widely used by many researchers mostly in developing countries, after it received many criticisms about how unrepresentative the threshold was to the budgets allocated to healthcare spending in every country (190). The WHO clarified the intent of the threshold, which was only to inform decision makers whether an intervention represented value for money, and not to be used on its own as a decision rule for reimbursing new technologies or setting prices. The WHO further recommended that decision makers should not base their decisions on a single cost effectiveness threshold but consider other factors such as fairness and affordability.

Category 6: Other

All the studies but two stated source of funding. With the exception of one study that was funded by a researcher, the remaining were funded by international agencies/bodies such as the Bill and Melinda Gates Foundation, or the 7th Framework Program of the European Union and United Nations Children's Emergency Fund. Seven studies did not declare a conflict of interest,

leaving the reader to speculate about the objectivity of the analyst. Of these studies, one evaluated diagnostics, one was on screening, three concerned treatment interventions and the remaining two evaluated pharmaceuticals. Worth noting is the fact that the pharmaceuticals that were evaluated were off patent and effectiveness data was sourced from published literature.

5.3.4 Usefulness of economic evaluation findings for decision-making

The methodology and findings of the eight studies that evaluated antimalarials were compared to evaluate their usefulness in guiding the decision maker on what intervention to prioritise for its management in Ghana. There were variations in the cost parameters included in the evaluations of antimalarials by different studies, even though the differences were not related to the perspective of analysis. For example, for the three studies evaluating chemoprophylaxis for malaria treatment, while two (175, 177) included the staff salaries as productivity time lost to the intervention; the remaining (173) did not.

There werealso differences in the classification of children under 5 years. The definitions ranged from 3-59 months (175, 177), 6-59 months (174) and 2-59 months (178). Paintain et al. (179) did not define children under five years and Tawiah et al. (169) evaluated only children under 24 months. In addition, different time horizons and effectiveness outcomes were used by each study (see Table 5-1). For instance, Ansah et al. (167) used correctly treated fever, Nonvignon et al. (177) used additional number of malaria cases and deaths averted, and Abotsi et al. (173) used DALYs averted.

5.3.5 Labour and data capacity for HTA in Ghana

One hundred and sixty-six persons were identified as authors from the 26 studies reviewed, an average of approximately six (n=6) per paper. Fifty-nine (n=59) out of 166 persons were local authors. However, only 36 authors had their roles in the study described. Figure 5-4 presents

the number of local persons who had a particular role in the studies reviewed. Only eight of them were lead authors. The majority of local authors were involved in data collection (n=32) and conceptualisation of studies (n=22).

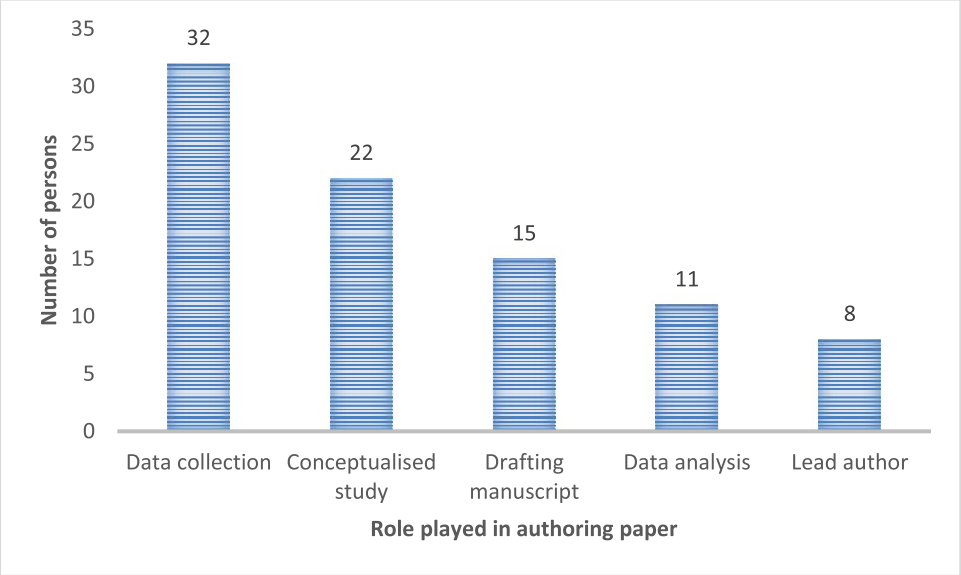


Figure 5-4: The roles played by local persons in reviewed studies

The sources of data used for the evaluations were deemed to be of good quality. The main source of effectiveness data were mainly from Ghana, and were derived from a single study (randomised controlled trial or before and after study) or program, with the exception of 10 studies (163, 164, 170-172, 182, 183, 185-187). In addition to the primary data source, some of the studies relied on international literature for additional information on their effectiveness data. The studies that did not use local effectiveness data did not report factors that might have affected the translation of data from elsewhere to the Ghanaian population, neither did they report the methods used to address this.

Similarly, with the exception of two (165, 186), all the studies relied on cost data from Ghana. The cost data were derived from trials, programs, NHIS pricing list for medicines and tariffs, and health facilities cost records. The studies that did not use cost data from Ghana had no local

person as a co-author. Other forms of data that could not be obtained in Ghana were sourced from international literature. These data include epidemiology of disease, cost of items not available on the Ghanaian market, death rates and life expectancies of the population under evaluation. For studies where effectiveness and cost data were not derived from a clinical trial or program, resource use was estimated with input from at least one local person, with the exception of two (165, 186) that based all its estimates (including resource use and costs) on international references. Prices of resource use were derived from the international price reference list and the WHO price list.

5.4 Discussion

While there were few economic evaluations conducted in Ghana between 1980 and November 2018, the quality of those evaluations was relatively high. One limitation of the studies, however, was their failure to characterise heterogeneity in the study population.

5.4.1 Scope and quantity of studies

The scope of diseases evaluated was broad considering the number of studies published over such a long period of time. Interventions aimed at preventing and treating malaria, the number one cause of death in Ghana, were the most commonly evaluated (n=8) followed by maternal and health conditions in children under 5 (n=8) which are also one of the Ghanaian health system's priorities. Contrary to the findings of Teerawattananon et al. (191), who reported on the lack of economic evaluation for 15 of the 20 highest disease burdens in the Thai setting, the results of this review indicate that the few EE studies conducted in Ghana are relatively responsive to the disease burden of the country. The review also indicated somewhat of a balance between publications concerning communicable (n=11) and non-communicable (n=15) diseases currently evident in the country. It is also worthwhile to note that these evaluations covered only primary health care (basic and essential health services) for universal

health coverage. Very expensive health technologies (such as renal haemodialysis) that often leads to patient and family impoverishment (192) were not evaluated and are also not covered under the NHIS. This supports the focus of the GNMP to appraise expensive technologies.

The increase in recognition of economic evaluation studies and their use in health systems around the world might be expected to be accompanied by growth in the number of publications; however, this is not seen in the Ghanaian setting. The 26 economic evaluations undertaken in Ghana is low compared to the number conducted in other developing countries, for instance, India (n=104) (193), South Africa (n=45) (194), Thailand (n=39) (191) and Vietnam (n=26) (195). It is, however, better than those reported for Bangladesh (n=12) (196), Nigeria (n=10) (197), and Zimbabwe (n=3) (198).

Although the reasons for the low number of evaluations in Ghana are not altogether clear, there is currently no formal policy mandating the use of economic evaluation studies for decision-making, nor is there a formal HTA agency in Ghana. Thus, economic evaluation has not been part of the process of adopting health technologies or making general decisions in resource allocation in the Ghanaian setting. As plans to introduce HTA progress (37) however, assessment of the local capacity to conduct economic evaluations becomes more pressing.

The use of EE studies for health decision-making has been associated with increased ease of accessing such evidence. However, none of the 26 papers reviewed were published in a local journal[22]. This leads to limited access to the information local people are likely to find most useful. Also, many journals require a paid subscription, which limits access. It is also worthy of note that some of the local journals require paid subscriptions for access, but these are more

[22] There is one peer-reviewed professional journal, Ghana Medical Journal that has been in publication for the past decade and is targeted at medical professions, some of who are decision makers. It is the journal where some cost of illness studies and other health economics related and social science research in health conducted in Ghana have been published over the years.

affordable than international journals, hence more accessible by decision makers and other users who may want to use it. This observation is quite similar to other findings reported in developing countries that also report a small proportion of economic evaluation studies published in local journals. These include Nigeria (14%) (197), India (20%) (193), Vietnam (23%) (195), Thailand (33%) (191), Zimbabwe (35%) (198) and South Africa (44%) (194). To make these studies easily accessible, the MOH can create a repository of such studies (which they can put together through literature scanning) that will be accessible by everyone. This will remove financial barriers to access.

5.4.2 Quality of studies and the usefulness of their findings for decision-making

In contrast to studies conducted in developing countries such as India, Vietnam and South Africa (194, 195, 199) that used the QHES instrument to assess the quality of the papers reviewed, this study used CHEERS checklist. The CHEERS checklist was used because it is both comprehensive and recommended by ISPOR as a tool that authors and reviewers can use to check the quality of manuscripts submitted for publication. Although the stated purpose of these tools is different, both have criteria that essentially assess the same things. The scores produced by these instruments can be compared by converting the CHEERS score to a percentage. The converted mean CHEERS score for the articles reviewed in this study was 84, comparable to that reported in similar settings using the QHES: India (86) (199), South Africa (86) (194), and Vietnam (89) for internationally published papers only) (195).

The percentages of CUA (42%) and CEA (58%) found in Ghana differs from other developing countries where CEA is reported as the predominant type of economic evaluation. For instance, Zimbabwe, Vietnam, Bangladesh, Nigeria, South Africa, Thailand and India, reported 100%, 96%, 83%, 90%, 78%, 66%, and 64% of studies reviewed as CEA respectively (191, 193, 195, 197, 198). The prevalence of CEA studies in most developing countries has been attributed to the lack of country specific utility weights and the complexity of undertaking other forms of

evaluation such as CUA and CBA which may require more expertise than is available in these settings (191, 193, 195, 197, 198). That said, the difference seen in the pattern of the type of economic evaluation studies between Ghana and other developing country settings could be attributed to the involvement of a high number of lead authors residing in developed countries, who may had the skills to conduct a CUA.

The provider perspective of evaluating health technologies conducted in Ghana was predominant and this can be attributed to the fact that most of these studies were funded by donor agencies, thus targeted at the payer whose interest is in how much it will cost to implement an intervention and its benefits. Of note is the inconsistencies in how studies defined their perspective of analysis based on the costs included in their studies. For example, while a some claimed a societal perspective (n=12) on the basis of including indirect costs such as productivity loss to patient and family, others (n=7) did not claim a societal perspective because of including indirect costs in their evaluation. However, this thesis notes that any costs incurred is a cost to the society irrespective of whom they fall on.

The time horizon for economic evaluation studies should be such that they capture all relevant costs and consequences needed to establish the effectiveness of a technology. EE studies reflect long-term consequences of a decision (160), hence under-or-over-estimation affects the outcome results which consequently impact on decision-making. The proportion of studies in Ghana that estimated costs and consequences over a lifetime (23%) is similar to Prinja et al. (193) who found that 21% of economic evaluations studies conducted in India were over a lifetime. The remaining studies however may have over- or under- estimated the costs and consequences of the technology evaluated, most especially those that estimated the costs and consequences for only the clinical trial/program/intervention periods (some of which were under one year). This is because the costs and consequences of most health interventions go beyond the period of implementation and data collection.

DALYs were the most commonly used health outcome measure which accords with what is recommended in the literature for use in developing countries (93, 95, 96). Although, the choice of measurements for determining outcomes was well chosen and robust, there were variations between similar interventions, and across different interventions. Therefore, a decision maker seeking to prioritise interventions according to available resources will face a difficult task since comparability is impossible. Consequently, this hinders the usefulness of existing economic evaluation studies on their own for decision-making purposes. The differences in the cost parameters included in estimating resource use (especially for studies evaluating the same condition), and inconsistencies in terminologies such as children under five and subsequent composition of population included in the evaluation further compounds this situation as the population included affect the ICER with which a decision can be made.

In estimating costs associated with resource use, it was observed that the source of cost data used by authors was dependent on the existence/availability of such data locally, its accessibility and convenience. In terms of convenience, a study was more likely to use local cost data when one of the authors was residing in Ghana. Only two studies, that had no local person as an author, did not use costs specific to Ghana, but relied on an international referencing price. Local cost estimates reflect the real cost of the intervention in the local context thus fostering accuracy and therefore acceptability of results by local users/decision makers. On the other hand, international reference prices are not a true representation of the cost of items locally, as the local market prices are affected by the foreign exchange rate and other costs involved in importation, hence often higher than international reference prices. Therefore, it is prudent that costs used in economic evaluations are reflective of the local context.

Although all 26 papers outlined the analytical approach, the 12 that failed to specify the use of a model in estimating the cost effectiveness of an intervention left readers wondering how all

resources and estimates used for the evaluation were captured with no clear outline of the disease's natural pathway. The absence of a model was more common in studies where local researchers played the lead role. This could be attributed to the limited skills in using a model for economic evaluation among Ghanaian researchers. Another methodological flaw worth mentioning is that, of the fourteen (n=14) papers that used a model, only six (n=6) included a structural representation of the model in the published paper, thus raising questions about the transparency of some of the models. Most guidelines for reporting economic evaluation studies recommend a diagrammatic presentation of the model to enhance readers' and decision makers' understanding.

Univariate and multivariate sensitivity analyses remain the conventional approach for addressing the uncertainties surrounding economic evaluations. In recent years, with general developments in the methods of economic evaluations, additional approaches have been used including threshold analysis, scenario analysis and probabilistic sensitivity analysis (PSA) which allows for uncertain parameters in the study to be considered simultaneously and varied for specified ranges (200). Even though the majority of studies (n=25) handled the uncertainty surrounding their studies through a sensitivity analyses, some studies (n=12) may have inadequately characterised the uncertainty surrounding their key model/study parameters by conducting only a univariate sensitivity analysis.

A univariate sensitivity analysis fails to account for the combined effect of more than one parameter varied simultaneously, which could make a difference in the overall results. Drummond and Sculpher (200) suggest PSA as the preferred approach to characterising uncertainties surrounding an economic evaluation because this enables the structural assumptions within a model to be tested through the creation of a distribution of the cost effectiveness/utility ratio from specified ranges of key parameters concurrently. Only four studies, all model-based, conducted a PSA.

One pronounced methodological flaw of the majority studies reviewed (n=25) was their failure to characterise the heterogeneity of the sample. Performing a subgroup analysis provides information about variations in costs, outcomes and the relative cost effectiveness of the intervention for different subgroups in the population/sample which could affect the overall cost effectiveness estimated, and in turn, the decision made using such information (160). Costs and benefits may also be under or overestimated due to this, influencing the calculated ICER. Characterising the heterogeneity of the sample also gives the decision maker additional information on allocating resources to subgroups within the population under investigation. None of the systematic reviews carried out by researchers in other developing countries and discussed here reported whether the studies they reviewed characterised heterogeneity. This may be because these studies used QHES (which does not have a criterion to assess this).

One of the reasons given by decision makers for the mistrust and non-use of economic evaluation results is the influence of funding agencies, especially pharmaceutical companies because of their vested interest (201). Hence, declarations of conflict of interest and the role of funders in studies may influence judgements on whether such studies are conducted independently. Failure of researchers to declare any conflict of interest where one exists, especially in instances where the evaluation concerns pharmaceutical intervention, could make room for potential users of such evidence to discredit it. Even though seven of the papers reviewed here did not include any declaration of conflict of interest, it is unclear if a pharmaceutical company funded any of these studies. It is worth noting that, five of these studies evaluated non-pharmaceutical interventions.

5.4.3 Labour and data capacity for HTA in Ghana

An average of six authors wrote the articles reviewed which is similar to that reported for India (6.22 authors) (193) but is higher than those of other African countries such as South Africa (3 authors) (194), Zimbabwe (3 authors) (198) and Nigeria (4 authors) (197).

Using the number of local persons who authored the studies reviewed (n=59) as a proxy for the human resource capacity available to conduct such studies, and to train others to do same, in Ghana capacity is limited. This is because even though the number seems big, those that were reported to be involved in the conceptualisation and actual analysis of data constituted less than 50% of the total. This limited human capacity could explain the limited number of studies undertaken and published.

Sources of data used were of good quality and mostly context-specific. The most common source of cost data that could be used for future economic evaluations was from the NHIS: NHIS medicines and tariffs list. Using the NHIS as a source of cost data will ensure consistency in findings of evaluations. However, there is the need for the country to invest more into data collection and storage as this review has shown that data from NHIS is not sufficient to address the needs of researchers.

5.4.4 Limitations of the review

A limitation of the review is that, only one person (the PhD candidate) conducted the screening of identified papers and extraction of data from the papers included in the final review. Best practice requires that a second independent reviewer screen and extract data from identified papers. However, this could not be done as the PhD candidate wanted to maintain independence in producing research output for this thesis. Nonetheless, thesis supervisors reviewed data extracted and interpretations from it.

The quantity of economic evaluation studies reviewed may have been underestimated because the literature search was limited to only international databases. Unpublished workshop, symposia and seminar presentations, grey literature such as unpublished government reports, and masters and doctoral thesis that are not indexed online were not captured.

Also, although the review was undertaken using a checklist and an annotated data extraction tool, the results may be biased because the assessment was undertaken by one reviewer and was subject to her interpretation of the checklist criteria. Further, the lack of clarity in the description of methodology and results of some of the papers reviewed may have impaired the quality assessment by the reviewer. However, to minimise the effect of these limitations, the reviewer conducted the review on two separate occasions and attempted to reconcile any discrepancies.

Another limitation concerns the checklist that was used to assess the quality of studies. As initially acknowledged at the methods section, the CHEERS checklist was developed with the aim of ensuring good quality conduct and reporting of EE studies, and not necessarily for assessing the inherent quality of EE studies. However, the thesis adopted CHEERS checklist to assess the quality of studies under the assumption that the quality of an EE study was dependent on the methodological approach used and subsequent reporting. Also, it is comprehensive, and currently recommended by most international journals on health economics for reporting economic evaluation studies. Because the development of the CHEERS checklist was not purposely for assessing the quality of EE studies, it fails to capture some quality measures such as the quality of data used. That said, it is worth noting this limitation as similar to other checklists available in the literature both for assessing the quality of EE studies (QHES instrument (161)), and for reporting EE (Drummond et al.'s checklist (8) and CHEC checklist (162)). These checklists focus on assessing all methodological issues and not the quality of evidence included for the evaluation.

Lastly, the use of the number of local persons who authored a study as a proxy for the human resource capacity available to conduct and teach economic evaluation of health interventions may have led to over- or under estimation of what is really available. This is because not all studies fully described the role of each author. It may also be the case that there are some other local persons available who were not captured because their work may not have been published yet, work in an area other than health, or were not captured in the literature search conducted. It is also possible that some Ghanaians have the relevant capacity and expertise in economic evaluation but their work did not include Ghana as the research site.

5.5 Conclusion

This chapter has presented and discussed the technical capacity of Ghana for the adoption of HTA. The available economic evaluation studies in Ghana are of good quality but are few in number, and cannot be used on their own for health decision-making because of differences in methodological approaches. This creates an opportunity and justification to introduce a comprehensive and systematic approach such as HTA that pulls together all applicable clinical and economic evidence as well as looks beyond these evidence to make recommendation for decision-making.

However, there appears to be limited human capacity to conduct HTA when the number of local persons who were involved in the studies are used as a proxy, which when considered together with the limited economic evaluation studies available, brings to light several issues that can be anticipated to affect the ability to conduct HTA in the Ghanaian health system. The evidence suggests the need to increase human and data resource capacity for HTA. This is not to say that Ghana cannot undertake HTA at all under the current circumstances, as recent literature has reported success in conducting HTA in countries that have limited human capacity, through collaboration with experts from other countries. Nonetheless, the next

challenge that needs addressing is the unavailability of data that could be used to do it. Therefore, the next chapter explores if economic evaluation studies from other countries could be used in an HTA in Ghana. It also investigates how economic data such as the clinical effectiveness of a technology and utility estimates could be transferred from other countries to conduct an economic evaluation for use in Ghana for HTA, in addition to local data.

This chapter contributes to guidance on future developments such as strengthening of methodological approaches used, building consensus on an appropriate method of reporting EE and for the planning of an HTA appraisal system.

6 HTA IN GHANA: JUSTIFICATION FOR CASE STUDY AND IDENTIFICATION OF DATA

6.1 Introduction

In Chapter 2, HTA processes in selected countries were appraised to assess their applicability to the Ghanaian health system. The appraisal revealed the importance of pursuing the establishment of a context-specific HTA agency. Subsequently, in Chapters 3 and 4, the current decision-making process in the Ghanaian health system was reported together with recommendations from decision makers on how the processes could be improved, including considering methods such as HTA for decision-making. However, the initial findings from Chapter 5 demonstrated that currently, and for some time to come, Ghana will need to rely on data from other countries to conduct HTA. These data include but are not limited to economic evaluation studies, clinical efficacy data and utility estimates.

This chapter introduces the remaining chapters of the thesis, which collectively assess the applicability, and transferability of data from other countries to the Ghanaian context for the purposes of HTA. This chapter starts by presenting a health technology of interest which was identified as suitable to demonstrate the use of data from other sources in a HTA for Ghana. In Section 6.2, the reasons for the selection of the case study are discussed and justified. As required in the conduct of HTA, Section 6.3 summarises a systematic review carried out to identify studies evaluating the chosen technology. Section 6.4 assesses their transferability to the proposed HTA appraisal in Ghanaian health system and provides justification for conducting a new economic evaluation for the HTA. Subsequently, the data needed to conduct the economic evaluation were identified and are presented in Section 6.5 The main findings of this chapter and implications for the next chapters are summarised in the conclusion, Section 6.6.

6.2 Choice of case study

The case study chosen for this thesis was selected with the main aim of assessing the transferability and generalisability of data from other countries for HTA in Ghana. The HTA conducted in this thesis is not intended to inform decision makers on the adoption of a new technology, nor is it meant to generate evidence for disinvestment of old technologies. It is expected that the results from this HTA appraisal will contribute to the general discourse on methodological and health system factors necessary for consideration in the formal introduction and use of HTA for decision-making in the Ghanaian health system.

6.2.1 Rationale for selecting a condition for the case study

Breast cancer was purposely selected as a case study to explore the challenges associated with generalising and transferring data from one setting to the other. In particular, it is important because there are differences in the epidemiology of breast cancer among women in developing countries, especially Africa, and those in high-income countries.

First, while the incidence of breast cancer is higher in developed countries compared to developing countries, the mortality rates are higher in developing countries. The differences in the survival of patients with breast cancer in the two settings have been attributed to the fact that developed countries employ early detection through widespread mammographic screening, and women diagnosed are able to access the best available treatment such as adjuvant systemic therapies (202). In most African countries, including Ghana, access to breast cancer screening and newer and more effective treatments such as hormonal therapies (203) are limited, contributing to the poor survival rates of breast cancer patients. This is because newer patented drugs are very expensive, rendering them unaffordable.

Second, and contributing to poorer breast cancer survival rates, most women in developing countries present at later stages of the cancer: stage III and IV (204), compared to their

counterparts in developed countries who present at earlier stages (I and II) of breast cancer (202). In Ghana, about 85% of breast cancer cases are presented late, that is, at stage III or IV, resulting in a poor prognosis (205).

Third, breast cancer is common among postmenopausal women in developed countries while for developing countries pre- and peri-menopausal women are most likely to present with the condition. For example, African women present with breast cancer on average 10-15 years earlier than women in high-income countries (206). Vanderpuye et al., (207) in an update of breast cancer management in Africa reported a mean diagnosis age of 46. Other studies published in Sub-Saharan Africa have also reported the incidence of breast cancer as common among pre-menopausal women with the peak age for diagnosis ranging from 30-49 years (208, 209). In Ghana, the mean age at diagnosis is 49 years (205, 210, 211) and the proportion of breast cancer among pre-menopausal and postmenopausal women in Ghana is 73% and 27% respectively (205). Table 6-1 presents a summary of the differences in the epidemiology and presentation of breast cancer between developed countries, developing countries and Ghana.

Table 6-1: Comparison of the characteristics of breast cancer in women between developed countries, developing countries and Ghana

Characteristics	Developed countries	Developing countries	Ghana
Age of diagnosis	Postmenopausal	Pre-and peri-menopausal	Pre-and peri-menopausal (mean age of 49)
Stage of presentation	Stages I and II (early breast cancer)	Stages III and IV (advanced breast cancer)	Stage III and IV (85% are advanced breast cancer)
Incidence compared to mortality	Higher incidence rate but lower mortality rate	Lower incidence rate but higher mortality rate	Lower incidence rate but higher mortality rate
Factors influencing survival	▪ Early detection and treatment ▪ Access to needed, newer and more effective treatments	▪ Late detection and treatment ▪ Limited access to the needed, newer and more effective treatments	▪ Late detection and treatment ▪ Limited access to the needed, newer and more effective treatments

6.2.2 Justification for the health technology chosen to be appraised for the treatment of breast cancer

Treatment of breast cancer is dependent on the hormone receptor status of the tumour, the menopausal status of the patient and the stage of cancer. Some types of breast cancer cells have receptors that attach to oestrogen or progesterone, which makes them grow faster. These cancers are referred to as hormone receptor positive cancers (oestrogen receptor positive (ER+) or progesterone receptor positive (PR+)) and constitute a higher percentage of all breast cancers diagnosed around the world. About 60-70% of women diagnosed with breast cancer are ER+, while 65% are PR+ (212). In Ghana, approximately 60% of women diagnosed with breast cancer are hormone receptor positive (47% ER + and 13% PR +) (205).

Hormonal therapy, used as an adjuvant (after surgery), neo-adjuvant (before surgery) or complementary treatment, controls the production of oestrogen and progesterone and slows down the growth of the cancer cells. Adjuvant treatments with hormonal therapy post-surgery, for hormone receptor positive breast cancers detected in their early stages, improves survival rates. Use of hormonal therapy in advanced stages of breast cancer also slows its progression. Therefore, hormone receptor positive breast cancers have better prognosis than hormone receptor negatives. Consequently, breast cancer detected in its early stages and are hormone receptor positive have better survival rates than those detected later or that are hormone receptor negative. Hormonal therapies include anti-oestrogen drugs (e.g. tamoxifen), aromatase inhibitors (e.g. anastrozole, exemestane, letrozole) and human epidermal growth factor receptor 2 (e.g. trastuzumab).

Figure 6-1 presents the hormonal treatment protocol for Ghanaian women with hormone receptor positive breast cancer. It is worth noting that the current Ghanaian standard treatment guidelines do not provide the clinical treatment management algorithm for breast cancer in Ghana, therefore the inputs from a Ghanaian clinical expert were used to ascertain this (see

Appendix 5, Figure 11-4 for details). Ghanaian women with hormone receptor positive breast cancers are given tamoxifen or both tamoxifen and anastrozole depending on their menopausal status as exhibited in Figure 6-1. Exemestane, which is not funded by the NHIS, is used only when patients are unresponsive to tamoxifen or anastrozole and are able to afford it themselves. The Food and Drugs Authority (FDA) approved all three drugs for use in Ghana for hormonal treatment of breast cancer. Both tamoxifen and anastrozole are reimbursed under the NHIS.

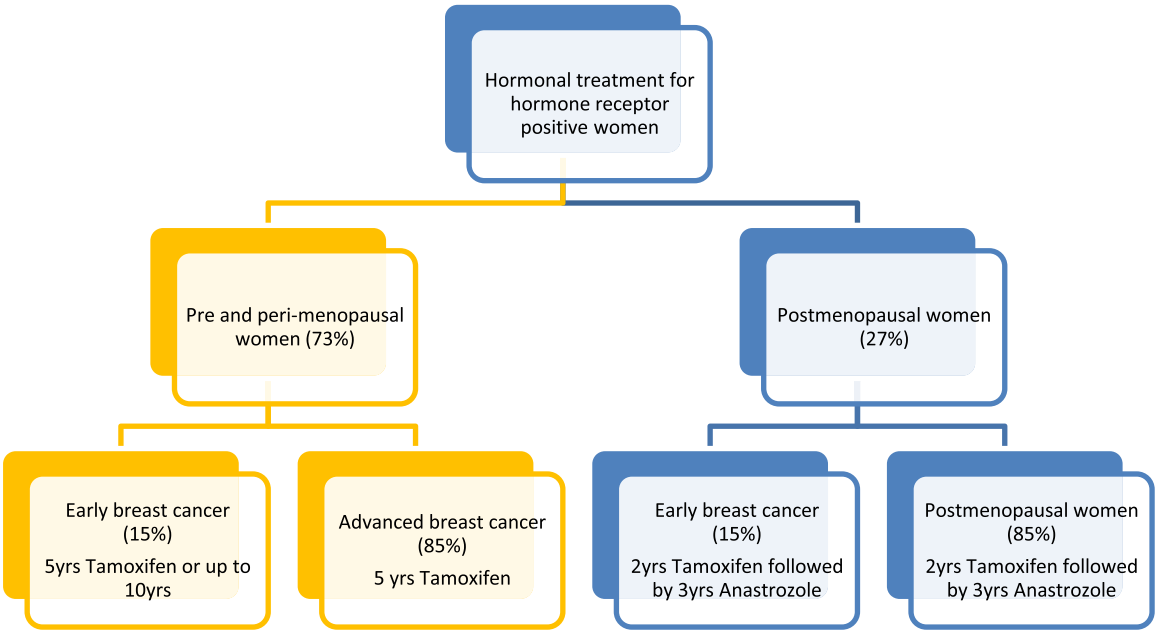


Figure 6-1: Hormonal treatment of breast cancer in Ghana

Based on the epidemiology of breast cancer in Ghana, this research focuses on the HTBC in pre- and peri-menopausal women. Consequently, tamoxifen for the HTCB is the health technology chosen for this case study. In early breast cancer, hormonal therapy is used as an adjuvant treatment. For advanced breast cancer, it can be used either as adjuvant treatment in instances where patients are treated with chemotherapy prior to hormonal therapy or as part of treatment when the cancer has metastasised to an extent that chemotherapy or surgery is not possible.

Tamoxifen is an anti-oestrogen drug, which acts by blocking oestrogen receptors in the breast cancer cells alone and stops or slows its growth. However, it acts as oestrogen in other tissues such as the uterus and bones. It is therefore called a selective oestrogen receptor modulator (SERM). Five years intake of tamoxifen reduces annual recurrence of breast cancer by 39% and mortality due to breast cancer by 31%, which corresponds to reducing the risk of recurrence of breast cancer and death by 15 years (213). These are further reduced by 2.8% when tamoxifen is taken for ten years (214, 215).

Tamoxifen was selected for this case study because, in addition to the reasons discussed above, it is recommended for the adjuvant and/or hormonal treatment of both early and advanced breast cancers in pre-menopausal, peri-menopausal and postmenopausal women. Its broad indication and low acquisition cost further strengthens its suitability as a candidate for this study in conducting an economic evaluation in Ghana, where the age distribution of breast cancer is predominantly pre- and peri-menopausal women.

Tamoxifen is a WHO essential medicine for the treatment of breast cancer, but is not on the Ghana essential medicines list. However, unlike other medicines that are not on the Ghana essential medicines list, tamoxifen is funded by the government under the NHIS for the treatment of breast cancer, under so-called special considerations. The Ghanaian government funds only two cancers under special considerations: breast and cervical cancers. Some of the reasons for this include that the diseases affect women, and are the numbers one and two causes of cancer deaths in Ghana (205). Therefore, under the current situation in the Ghanaian health system where there have been calls for inclusion of other cancers such as childhood cancers in the special benefit scheme, the findings of this appraisal could be used as justification for funding breast cancer treatment. It will also provide decision makers with information on the financial impact of funding tamoxifen, for the purposes of financial planning for the NHIS budget.

Another justification for using tamoxifen for the HTA appraisal is that it is no longer patented, thus several generic brands are available on the market at relatively low acquisition prices. However, in Ghana, the market price of tamoxifen is highly determined by foreign exchange rates, just as all supplies that are imported. A depreciation in the Ghanaian cedi (GHC) results in an increase in the prices of all imported goods (216-219). Hence, the price of tamoxifen may not depreciate with an increase in the production of generic brands as might be expected. Consequently, the current reimbursement price of tamoxifen is lower than the current market price, as the Ghana cedi has depreciated since the last review of NHIS reimbursement prices[23].

As a result, even though the government under the NHIS funds tamoxifen, patients pay out of pocket to cover the difference. Meanwhile, under the NHIA Act 852 (220), patient co-payment is not a funding arrangement of the NHIS, as the Act mandates that the scheme will pay the full costs of treatments for conditions listed under the benefit package. However, due to the characteristics of the Ghanaian market mentioned above and providers protecting themselves from loss, patients are 'forced' to make 'informal' co-payments until such time as the reimbursement prices of the NHIS are reviewed and modified to be consistent with the current market price of tamoxifen. This situation provides an opportunity to explore the implications of the price instability of medicines in the Ghanaian market for government funding and to investigate the possible role HTA can play in pricing and negotiation of prices of medicines in Ghana.

Course of tamoxifen therapy

In the adjuvant breast cancer setting (and treatment for advanced breast cancer in some instances), some international breast cancer treatment guidelines have recommended that pre-menopausal women with early breast cancer receive tamoxifen for 5 years or up to 10 years

[23] The most current reimbursement price list in use was compiled in 2016 for use for years 2016/2017 using data collected in 2015. As at the time of this evaluation, this list was in use.

depending on the menopausal status of the woman after year five (212, 221). Even when women remain pre-menopausal after the first 5 years of tamoxifen therapy, the National Comprehensive Cancer Network (NCCN) recommends cessation of tamoxifen or continuation for up to 10 years, depending on factors such as the preferences of women (212). This is because recent studies have reported some additional benefits when tamoxifen is taken for 10 years. However, the data available do not exhaustively justify a complete change from 5 years to 10 years tamoxifen therapy as data on the additional effectiveness of tamoxifen beyond 10 years is still under collection (212). Hence, there is uncertainty surrounding the additional benefits of 10 years tamoxifen treatment outweighing the decreased quality of life due to adverse events.

Tamoxifen is time restrictive because beyond ten years, there is no additional benefit of tamoxifen to the patient considering, meanwhile the patient would continue to experience adverse effects while taking it, which will affect her quality of life and incur additional costs to the health system. Tamoxifen is also used in the hormonal treatment of metastatic breast cancer for both pre- and peri-menopausal women. In Ghana, tamoxifen therapy is recommended for a minimum of 5 years or more depending on the patient's health condition, tolerance and the stage of cancer.

Comparator for the appraisal

No treatment/watchful waiting was chosen as the comparator for the technology appraisal for pre- and peri- menopausal women. This is because in Ghana, women who develop breast cancer receive either treatment or no treatment depending on whether the woman attends a health facility to be diagnosed. In addition, it is assumed that patients who are uninsured (i.e. are not insured by either the NHIS or a private insurer) are unable to afford treatment, and thus do not receive any.

A possible comparator for this appraisal is anastrozole. It is the next choice of endocrine therapy for postmenopausal women in Ghana if the use of tamoxifen is contraindicated, or after two years of tamoxifen. However, it is not used for this appraisal because anastrozole is only indicated for the treatment of postmenopausal women. Other treatments used for hormonal therapy in breast cancer which equally qualify as possible comparator candidates for this analysis include other aromatase inhibitors (such as letrozole and exemestane), ovarian ablation and ovarian suppression (using drug therapy such as leuprolide and goserelin), or surgical removal of the ovaries (oophorectomy)). Letrozole and exemestane were not selected as comparators since they are mostly used for postmenopausal women.

Ovarian suppression and ovarian ablation were not selected as comparators for pre-menopausal women because these are not currently used as standard practice for the hormonal treatment of breast cancer in Ghana. This is because young African women who are still in their reproductive years rarely accept any form of treatment that will eliminate or suppress ovarian function (207). Consequently, treatments such as ovarian function suppression or ablation or the prescription of aromatase inhibitors for hormone receptor positive women is not used in these settings. Therefore, the most commonly accepted hormonal therapy for pre- and peri-menopausal African women is tamoxifen (222, 223).

Finally, toremifene, a SERM, was not used as a comparator because it is indicated for the treatment of metastatic breast cancer alone in postmenopausal women, and it is not used in Ghana. The next section presents a summary of the existing literature on economic evaluations of tamoxifen for the ATBC.

6.3 Summary of literature on economic evaluation studies on tamoxifen

To conduct an economic evaluation, it is recommended practice to review the literature on existing evaluations of the technology under study. This enables the evaluator to identify

relevant information such as model structures and sources of data used, which are used to inform the structure and input parameters of the current model.

A systematic literature search was used to identify economic studies that evaluated the cost effectiveness of tamoxifen compared to no treatment/watchful waiting for the HTBC. The review also sought to identify the sources of data (both economic and clinical) used in these evaluations. Subsequently, the review investigated the applicability of studies to the Ghanaian context.

Four databases and five HTA agency websites were systematically searched using keywords such as "cost utility analysis", "cost effectiveness analysis", "economic evaluation", "tamoxifen", "hormonal therapy", "adjuvant treatment" and "breast cancer" (See Appendix 5 Table 11-5 for a list of databases) for which a total of 1827 citations were identified. After abstract and full text screening, 32 studies compared tamoxifen to another treatment, but only one study evaluated the cost effectiveness of tamoxifen compared to no tamoxifen for the HTBC in pre-and peri-menopausal women. Of the 32 studies, 20 were potentially applicable to the Ghanaian setting overall (that is studies that looked at anastrozole for the treatment of postmenopausal women), hence, were included in the final qualitative review[24] (see Appendix 5 Table 11-5, for a summary of the identification process).

Table 6-2 presents a brief description of the characteristics of studies included in the review. A detailed description of these studies including their methodological approach (such as source of efficacy estimates, utility weights used, model structure), results and limitations is detailed in Appendix 5, Table 11-6, Table 11-7, Table 11-8 and Table 11-9).

[24] These studies were included in the review even though they did not pertain to the population for this evaluation (pre- and peri-menopausal women), because it enabled me to review other breast cancer economic evaluation studies in the adjuvant setting such as model structure and source of data.

Table 6-2: Some Characteristics of studies included for qualitative review

Study	Country	Population	Comparators
Early breast cancer			
Hillner (2004)	USA	ER +ve PMW (mean age 64yrs)	Anastrozole 1mg dly/ Tamoxifen 20mg dly
Gil et al. (2006)	Spain	ER +ve PMW with operable cancer (mean age 63yrs)	Anastrozole 1mg dly/ Tamoxifen 20mg dly
Lonning (2006)	Norway	Lymph node -ve and node +ve PMW (mean age 55,65,75 yrs)	Anastrozole 1mg dly/ Tamoxifen 20mg dly
Moeremans and Annemans (2006)	Belgium	HR +ve PMW (mean age not specified)	Anastrozole 1mg dly/ Tamoxifen 20mg dly
Rocchi and Verma (2006)	Canada	HR +ve PMW (mean age 64yrs)	Anastrozole 1mg dly/ Tamoxifen 20mg dly
Locker et al. (2007)	USA	HR +ve PMW (mean age 64yrs)	Anastrozole 1mg dly/ Tamoxifen 20mg dly
Mansel et al. (2007)	UK	HR +ve PMW (mean age 64yrs)	Anastrozole 1mg dly/ Tamoxifen 20mg dly
Skedgel et al. (2007)	Canada	HR +ve PMW (mean age 60yrs)	Anastrozole 1mg dly/ Tamoxifen 20mg dly
Skedgel et al. (2007)	Belgium	HR +ve PMW (mean age 60yrs)	Anastrozole 1mg dly/ Tamoxifen 20mg dly
Younis et al. (2007)	Canada	HR +ve PMW (mean age 60yrs) nodal	Anastrozole 1mg dly/ Tamoxifen 20mg dly
Karnon, Delea and Barghout (2008)	UK	HR +ve PMW with invasive cancer (50% node +ve) (mean age 61yrs)	Anastrozole 1mg dly/ Tamoxifen 20mg dly
Fonseca, Araujo and Saad (2009)	Brazil	HR +ve PMW (mean age 64yrs)	Anastrozole 1mg dly/ Tamoxifen 20mg dly
Thomas et al. (2009)	UK	PMW with breast cancer relapse (mean age not specified)	Anastrozole 1mg dly/ Tamoxifen 20mg dly
Lee et al. (2010)	Korea	HR +ve PMW (mean age 50yrs)	Anastrozole 1mg dly/ Tamoxifen 20mg dly
Lux et al. (2010)	German	HR +ve PMW (mean age 64yrs)	Anastrozole 1mg dly/ Tamoxifen 20mg dly
Lux et al. (2011)	German	HR +ve PMW (mean age not specified)	Anastrozole 1mg dly/ Tamoxifen 20mg dly
Shih et al. (2012)	Singapore	HR +ve PMW (mean age 64yrs)	Anastrozole 1mg dly/ Tamoxifen 20mg dly
Advanced breast cancer			
Dranitsaris, Verma and Trudeau (2003)	Canada	ER/PR receptor +ve PMW	Anastrozole 1mg dly/ Tamoxifen 20mg dly
Simons, Jones and Buzdar (2003)	USA	HR +ve PMW (mean age not specified)	Anastrozole 1mg dly/ Tamoxifen 20mg dly
Both early and advanced breast cancer			
Yang et. al (2010)	Korea	All women diagnosed of cancer; age, nodal status and HR status (mean ages of not specified)	Tamoxifen 20mg dly/No tamoxifen 20mg dly

Abbreviations: dly: daily, ER: Oestrogen receptor, HR: hormone receptor, mg: milligram, PMW: postmenopausal women, +ve: positive, -ve: negative.

The studies were conducted mostly in high-income countries, predominantly in the USA (n=3), UK (n=3), and Canada (n=4). The type of breast cancer evaluated was predominantly early stage breast cancer (85%); and the type of evaluation was CEA, CUA, or both. Nineteen studies (n=19) compared the cost effectiveness of tamoxifen and anastrozole, with tamoxifen being the primary comparator in all cases. The remaining studies compared tamoxifen therapy to no tamoxifen therapy (224). In all studies, the treatments being investigated were in the first line of therapy and were used in a monotherapy treatment regimen administered for 5 years. The population of women used in the evaluations were largely postmenopausal, with the exception of one study (224) that evaluated all women with breast cancer in a retrospective analysis. Women with hormone receptor positive and oestrogen receptor positive breast cancers were the population groups most commonly included in the cost effectiveness analysis (Table 6-2). Discount rates used ranged between 5%, 3.5% and 3% for both costs and consequences, and 1.5% for only consequences (Appendix 5, Table 11-7).

With the exception of three studies (224-226) that conducted the evaluation from a societal perspective and one that did not specify the perspective of the analysis (108), the remaining perspectives were that of a payer. The payer perspective was either direct (227), healthcare system (228-241) or third party (242) (Appendix 5, Table 11-6). None of the evaluations were conducted as a pre-requisite for the reimbursement of tamoxifen/anastrozole. They were however estimated with those who make decisions on reimbursement and funding in mind, hence the dominance of a payer perspective approach to evaluation.

Most of the evaluations had a strong level of evidence for their clinical data – efficacy estimates. The efficacy estimates were based on the results of either a randomised controlled trial (RCT) or a meta-analysis of more than one RCT. Only one study (241) conducted a meta-analysis and used estimates generated for the evaluation. The remaining studies that used meta-

analysis data were those published by the Early Breast Cancer Trialist Collaborative Group (EBCTCG) alone (237) or in combination with results from one or more RCT (227, 228, 230, 235, 242). The EBCTCG is a collaborative group of researchers from around the world who continuously aggregate RCT data on the treatment of early breast cancer in a meta-analysis (243) to inform clinical and reimbursement decisions on the effectiveness and cost effectiveness of any intervention used in the treatment of early breast cancer.

Seventeen evaluations reported QALYs as the outcome measure, with all utilising health related quality of life data obtained from a different source than the efficacy estimates. The utility values were derived from either the published literature or studies conducted specifically for the evaluation. Whereas some evaluations described the methods used in the estimation of utility weights, others did not. Those that described the methods derived it from women with breast cancer (n= 4), the general population (n=2) or from experts (those working closely with women with breast cancer) (n=2).

The most cited source of utility weights by these evaluations is Sorensen et al. (244). They used a standard gamble approach to derive utility weights from 67 women (mean age 67.8 years) with early breast cancer in a cross-sectional study conducted in the UK (n=23) and the USA (n=44). Eight evaluations used utility values derived from the population of the study setting. Also, while some evaluations (n=8) used only one study for the utility weight as inputs to the model, others used more than one (n=6). However, it was not clear if a composite value was estimated for those that used more than one source of utility weights. Three studies used estimates from the CEA registry of the Tufts Medical Centre in Boston, USA[25]. Six evaluations used estimates derived from their setting. A detailed description of the utility weights used and their sources as well as methods of estimation is presented in Appendix 5, Table 11-8.

[25] http://healtheconomics.tuftsmedicalcenter.org/cear4/SearchingtheCEARegistry/SearchtheCEARegistry.aspx

A Markov model was the commonest method used (n=15) to synthesise clinical and economic data to establish the cost effectiveness of tamoxifen and its comparator. Most of the women from the evaluations entered the model at a mean age of 64 years according to the characteristics of the population of women who were enrolled in the trial. The cycle length for the evaluations ranged from monthly to quarterly, half yearly and yearly. The number of health states used in the models varied from ten to five, with seven being the most common. Table 6-3 presents the health states used by the studies. The time horizon also varied widely among evaluations. Resource use and associated costs were derived from study setting. There were variations in the cost per tamoxifen tablet used in these studies: 0.06, 0.17, 0.24, 0.42, 0.43, 0.54, 1.08, 1.35 and 3.33 per tablet in 2017 value, all in AUD.

Table 6-3: Summary of health states used by studies reviewed

Study	Number	Description
Hillner (2004)	7	▪ Well and receiving adjuvant treatment ▪ Loco-regional or contralateral breast cancer ▪ Systemic breast cancer recurrence ▪ Adjuvant treatment halted ▪ Vaginal bleeding or venous thrombotic embolism ▪ Hip fracture ▪ Death
Gil et al. (2006)	10	▪ Disease-free without complications ▪ Disease-free with complications ▪ Loco-regional breast cancer ▪ Recurrence with metastasis ▪ Fractures ▪ Endometrial cancer and other second neoplasms ▪ Deep vein thrombosis/pulmonary embolism ▪ Myocardial infarction ▪ Stroke ▪ Death
Moeremans and Annemans (2006)	4	▪ Primary treatment ▪ Loco-regional recurrence ▪ Metastatic disease ▪ Death
Rocchi and Verma (2006) Shih et al. (2012)	5	▪ No recurrence ▪ Loco-regional recurrence ▪ Distant recurrence ▪ Death from other causes ▪ Death from breast cancer
Locker et al. (2007) Mansel et al. (2007) Lux et al. (2010)	7	▪ On adjuvant endocrine treatment ▪ An unplanned switch to adjuvant treatment ▪ Off treatment and in remission ▪ Distant recurrence with local/regional recurrence

Study	Number	Description
		▪ Death due to breast cancer ▪ Death due to other causes
Skedgel et al. (2007a) Skedgel et al. (2007b) Younis et al. (2007)	5	▪ Well on treatment ▪ Well off treatment ▪ Local relapse (loco-regional and contralateral recurrences) ▪ Distant relapse ▪ Death (with or without relapse)
Karnon, Delea and Barghout (2008)	7	▪ Disease-free ▪ Contralateral tumour/remission ▪ Loco-regional recurrence/remission ▪ Soft tissue metastasis ▪ Bone metastasis ▪ Visceral metastasis ▪ Death
Lee et al. (2010)	6	▪ Disease-free ▪ Disease-free with adverse events ▪ Contralateral breast cancer ▪ Loco-regional breast ▪ Distant recurrence ▪ Death

The evaluation results were presented as cost per QALY gained or cost per LYS or both. The ICER estimates varied widely; $20,246 to $75,600 (237, 238), £11,428 to £17,656 (231, 234) and €1,495 to €94,648 per QALY gain/LYS (232, 237). While the reasons for the large differences in these results are not entirely clear, a number of model parameters could have contributed to this. There were consistencies in the direction of the impact of the time horizon over which an intervention is evaluated, the extent and duration of the benefits and the hazard ratio (HR) of disease-free state for the comparator, anastrozole on the ICER estimated. The impacts of other parameters such as discount rates and utility weights on the ICER reported by evaluations were inconsistent.

In conclusion, the characteristics of the evaluations and the models used were dependent on data available to the evaluator (including setting-specific cost) and the treatment protocols of the setting. However, in terms of utility values, it seems most studies relied on what had been reported in previous studies, without considering the original source, as the most cited study happens to be an abstract with no clear indications of how utility values can be estimated from

the composite value they reported. The next section reviews the applicability of the evaluations to the Ghanaian context.

6.4 Grounds for conducting a new economic evaluation for use in HTA – transferability of economic evaluation results to the Ghanaian setting

Many economic evaluations have been conducted on tamoxifen therapy for breast cancer patients but none have been undertaken in Ghana or Africa. In addition, these studies evaluated the cost effectiveness of tamoxifen therapy (as either adjuvant or usual treatment) for postmenopausal women with early breast cancer.

It is argued that the results of clinical trials are unlikely to vary across jurisdictions (245). However, to make clinical data context-specific most economists apply the observed trial-wide relative risk reduction for the health states of interest to the baseline risk in the setting of evaluation (246). This approach is able to address limitations such as differences in patient characteristics between clinical trial settings and other jurisdictions. Nonetheless, the challenge for this approach is identifying the country specific baseline risk data.

Economic data, on the other hand, cannot be easily transferred, thus limiting the adoption and use of results of economic evaluation studies of one setting to another. The factors that restrict transferability of economic data include differences in basic epidemiology and demography of a disease, relative prices and costs and population values that are expressed in health state preference valuations (8). Resource use and costs also vary between countries depending on their specific delivery, funding and reimbursement arrangements (247). Therefore, to make economic evaluation relevant to a jurisdiction of interest, country specific data on resource use, costs, epidemiology and the demography of disease as well as relevant health utilities should be used.

Consequently, results of economic evaluation studies from one jurisdiction are not applicable to another, unless some conditions have been satisfied. These include similar clinical practices and treatment patterns, relative prices and resource use, and preferably that the country is part of the multi-location site for clinical trial data (245, 246). From the review conducted in section 6.3, none of the evaluations can be applied to the Ghanaian context for the following reasons:

1. Ghana (or similar African country) was not one of the study sites for the clinical trials reported in the evaluations as sources of clinical efficacy data.
2. There is a difference between the demography and epidemiology of breast cancer in Ghana and the countries where these clinical trials (and evaluations) were conducted. For instance, whereas the population of women with breast cancer in these evaluations were predominantly postmenopausal with a mean age of 64 years, most women with breast cancer in Ghana are pre-menopausal with a mean age of 49. Only one evaluation assessed the treatment of pre-menopausal women.
3. Only three evaluations estimated the cost effectiveness of treatment for advanced breast cancer; two were published more than 10 years ago and the clinical practice reported varies from that used in Ghana. Meanwhile, 85% of all breast cancers in Ghana are diagnosed at an advanced stage.
4. There are significant differences between clinical practices and health resources available in Ghana compared to those in the evaluations, which were mostly conducted in high-income countries. Consequently, this will affect the resources used to estimate the ICER.
5. The relative prices and unit cost of resources vary between Ghana and the countries where the evaluations were conducted. For instance, whereas most evaluations reported about a 150% cost difference between tamoxifen and anastrozole, a difference of about 60% is observed in Ghana. This is largely because of the increase in the availability of

generic drugs in Ghana (and elsewhere) since these evaluations were conducted. Consequently, relative costs of interventions will vary from those in the evaluations.

6. Mortality and life expectancy rates differ widely between the countries in the evaluations and Ghana.

These reasons provide a strong rationale for a new economic evaluation to be conducted from the perspective of the Ghanaian health system, using country specific data as much as possible. The perspective of analysis represents the viewpoint from which the costs and consequences of an intervention are evaluated. A health system perspective of evaluation includes direct medical care costs, which include the intervention cost and follow-up treatment costs, and their accompanying consequences (in this case, benefits from the intervention) (8, 160). This perspective was chosen as the base case for the evaluation because the thesis sought to evaluate the cost-effectiveness of tamoxifen to the NHIS, which is the payer of health services, and represents the government. The costs included in this perspective for the analysis represent the costs paid by the NHIS. The NHIS reimburses providers (health facilities) for all the costs associated with treating an individual with a health condition (according to agreed protocol and reimbursement price) covered under the scheme. This is inclusive of the costs of consultations, diagnostics, medicines, surgeries, hospitalisation (including cost of treatment, accommodation and food) and costs associated with adverse events from medications and complications from diseases treated. In the next section, the process used to identify data appropriate for the Ghanaian model, and justification for their selection is described.

6.5 Identification of data for model

6.5.1 Clinical efficacy data

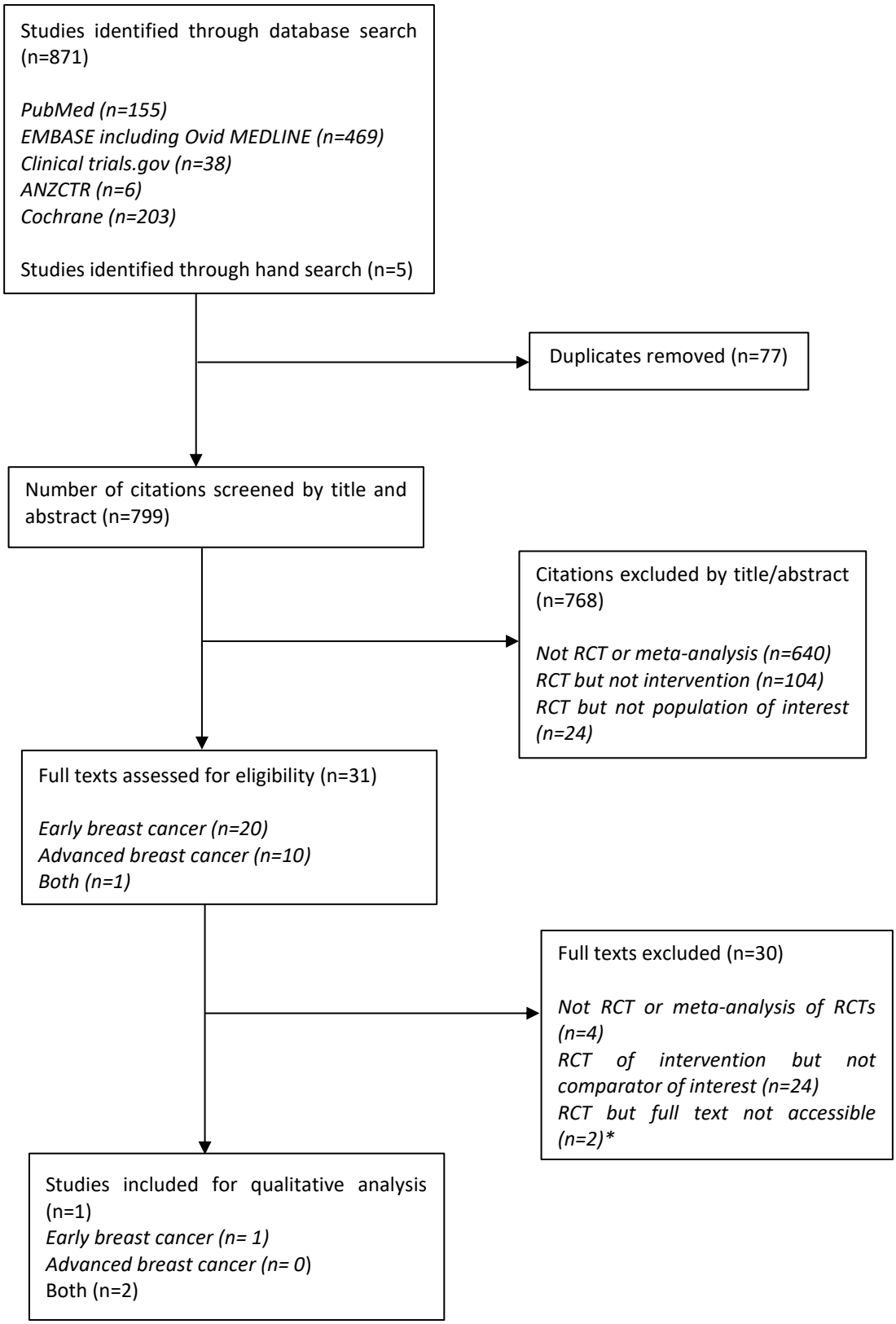
An extensive systematic literature search was conducted to identify studies reporting the clinical efficacy of tamoxifen for the HTBC in pre- and peri-menopausal women. The search

included all studies with one of the comparators being tamoxifen. The databases searched were Cochrane, EMBASE including Ovid MEDLINE, PubMed, clinical trials.gov and the Australia New Zealand Clinical Trial Registry. Key words used for the search included “breast cancer”, “peri-menopausal”, “tamoxifen”, “adjuvant”, “therapy”, “cancer treatment” “hormonal therapy” and “adjuvant treatment”.

Eight hundred and seventy-one (n=871) citations were retrieved from the databases, of which 799 were screened after removal of duplicates. Figure 6-2 shows a summary of the process used in identifying clinical trials reporting the effectiveness of tamoxifen for the treatment of breast cancer in pre-and peri-menopausal women. Studies were excluded from full text screening if they were not a RCT, meta-analysis of RCTs, did not consider tamoxifen as a treatment intervention for breast cancer or the population under study were not pre- and/or peri-menopausal women.

A meta-analysis conducted by the EBCTCG that summarised individual patient level data from 20 trials (n=21,457) in one study was chosen for the evaluation in this study. These trials investigated the effectiveness of tamoxifen (up to 5 years duration of therapy) versus no tamoxifen for the hormonal treatment of early breast cancer (213). None of those trials included in the meta-analysis involved Ghana. The only African country included as a centre for one of the trials was South Africa. However, due to lack of patient level data, it is not clear whether the characteristics of the patients from South Africa resembled the Ghanaian population in terms of mean age of onset of breast cancer and/or entry into the trial.

No study was identified from the search that compared tamoxifen with no tamoxifen for the hormonal treatment of advanced breast cancer among pre- and peri-menopausal women.



Note: *RCTs where full text were not accessible were those where abstracts were published as conference proceedings but full text was never published.
Abbreviations: ANZCTR: Australia New Zealand Clinical Trial Registry, RCT: randomised controlled trial.

Figure 6-2: Summary of process used to identify and select studies to inform the clinical efficacy of tamoxifen

Table 6-4 presents a summary of RCTs excluded from the qualitative analysis that have tamoxifen as one of the intervention under investigation, but for the purposes of this research, their comparators are not of interest. Of the ten studies included for full text screening for hormonal treatment of advanced breast cancer, two (n=2) were reviews, two (n=2) were abstracts only with full texts inaccessible and the remaining RCTs and meta-analysis (n= 6) compared tamoxifen to different strategies targeted to suppress ovarian function. For studies on early breast cancer included for full text screening, two (n=2) were reviews, seventeen (n=17) had tamoxifen as a comparator but included different strategies of ovarian function suppression such as surgical oophorectomy and medicines for ovarian ablation. One study (n=1) reported a meta-analysis of adjuvant and/or hormonal treatment of both early and advanced breast cancer in pre-menopausal women (see Table 6-4).

Table 6-4: Summary of characteristics RCTs with full texts accessible that had tamoxifen as one comparator but the alternative not intervention of interest

Study characteristics	Number of studies	
	Early breast cancer	Advanced breast cancer
Individual studies comparing tamoxifen with ovarian function suppression	15	3
Meta-analysis of studies comparing tamoxifen with ovarian function suppression treatments	0	1
Meta-analysis of adjuvant treatments for breast cancer in pre-menopausal women	2	2
Sub-total	*17*	*6*
Meta-analysis of adjuvant treatment of both early and advanced breast cancer	1	
Total	**24**	

NB: Studies reported treatment as adjuvant irrespective of the stage of cancer.

6.5.2 Outcome measure

Two common metrics used in CUA were discussed in Chapter 2, section 2.4.1. From the literature reviewed, it is anticipated Ghanaian decision makers will appreciate DALYs more than QALYs, as the former is commonly used in their setting for describing burden of diseases. However, in this thesis QALYs are used as a health outcome measure to assess the cost utility of tamoxifen for HTBC in the base case scenario, because QALYs are better suited for CUA

than DALYs. In addition, DALYs due to breast cancer are derived from generic disability weights for cancers in general, whereas QALYs are estimated from utility weights specific to the different health states in the natural history of breast cancer.

Furthermore, while adverse events due to tamoxifen can be adequately incorporated in the model as disutilities for QALYs, the same cannot be undertaken for DALYs without over-estimating the disability due to breast cancer. This is because some adverse events are captured as conditions on their own, some with disability weight values similar to or more than those due to breast cancer states. Thus, including disability weights due to adverse events of tamoxifen may double count the disability. For example, in a controlled phase of breast cancer (assumed to be synonymous to the disease-free state with no breast cancer state), where patients are on treatment, in this circumstance, on tamoxifen, the disability weight is 0.049. The disability weight due to mild osteoarthritis, one of the adverse events of tamoxifen, is 0.023. Therefore, the disability weight and subsequently the DALYs for patients on treatment with tamoxifen will be more than those who are not receiving tamoxifen, which is intuitively incorrect, as tamoxifen is supposed to improve patients' disability due to the condition, not worsen it.

In addition, there were concerns about double counting some parameters such as mortality rates and duration of the sequelae as these are accounted for in estimating DALYs averted, however are also part of the model structure. To take account of DALYs, they are used as a health outcome measure in a sensitivity analysis.

Utility and disutility data

Quality of life utility weights for breast cancer treatment were not collected in the trials identified for use as sources of clinical efficacy data for the models. Therefore, it was necessary to identify utility weights associated with the health states included in the model. First, the

utility weights used by economic evaluation studies on breast cancer treatment reviewed under section 6.3 were considered. None of these sources were deemed suitable for use because

1) Sorensen et al. (244), the most frequently cited source, is a conference abstract publication that only provides minimum and maximum utility values generated from women with breast cancer. It is, therefore, not clear how the studies that referenced the utility weights from this study derived the utility values for the various health states, as none of them elaborated on it.

2) The other studies elicited utility values from either patients or health personnel, which is not regarded as best practice.

3) Those that estimated utility weights from the general population had a small sample size (example n=25) and the population was not specific to Ghana or any African country (235, 241).

In lieu of this, a systematic literature search was undertaken in EMBASE and PubMed to identify health utilities and health related quality of life measures applicable to breast cancer treatment (early and advanced). The search included key words like “standard gamble” “time trade-offs”, ‘discrete choice experiments”, “preference weights”, “multi-attribute utility”, “utility weights” and “utility values”. A manual search of references and the cost effectiveness analysis registry at Tufts Medical Centre (which included individual studies) was conducted to identify additional studies on disutility weights. The results of the literature search are provided in Table 6-5.

The inclusion criterion was subsequent composition original studies reporting utilities of health states for breast cancer. Sixteen studies satisfied this criterion, with none of them specific to Ghana or Africa. Four studies out of these were included for use in this study: one for utility weights and three for disutility weights. The utility weight values used in this study were derived from the meta-regression analysis conducted by Peasgood et al. (248). This was deemed the most appropriate source of utility weight data in the absence of a country specific

one as it included 476 unique utility values; 230 usable ones for early breast cancer and 117 for metastatic breast cancer in the meta-regression analysis.

Table 6-5: Summary identification of utility weights for health states in breast cancer

Process of identifying studies	**EMBASE and PubMed**
Number of citations retrieved by search (after removal of duplicates)	1942
Number of citations excluded after title/abstract review	
Does not concern breast cancer for women	715
Concerns breast cancer but not on health state utilities	696
Reported/used health state utilities in studies but not original study	489
Total number excluded after title/abstract review	*1900*
Number of citations eligible for full paper screening for each database	42
Number of citations excluded after full text review	
Specific to a type of breast cancer or its treatment	15
No published data/full text not located	11
Total number of citations excluded after full text/abstract review	*26*
Number of citations included from full text screening	16
Number of full articles included through manual search of references and cost effectiveness analysis registry at Tufts Medical Centre (individual studies)	10
Number of citations included for use in the model	**4 (1 utility and 3 disutility)**

Peasgood et al. (248) conducted a systematic search of 13 databases and identified 49 articles that provided 476 utility values distinct for breast cancer. They conducted a meta-regression on the utility estimates identified from these studies using ordinary least squares, weighted by the number of respondents in each study as well as accounting for clustering within each study group. The meta-regression was conducted for utility estimates specific to early breast cancer and metastatic breast cancer separately. For early breast cancer, the meta-regression controlled for surgery, nonsurgical treatments, time period, who was surveyed and the valuation method used. The meta-regression model for metastatic breast cancer also controlled for treatment type, response to treatment, side-effects, population surveyed, and method of valuation.

Table 6-6 and Table 6-7 present the meta-regression results for both early and metastatic breast cancer. A description of the derivation of utility weights for each breast cancer state used for the economic evaluation conducted for this thesis, early and advanced breast cancer, are presented under the methods section of Chapters 7 and 8 respectively.

Table 6-6: Regression models for early breast cancer

Variables	Model 1	Model 2	Model 3
Surgery (breast conserving surgery)			
Mastectomy and reconstruction	-0.020	-0.029	-0.049
Mastectomy only	0.041	0.003	0.017
Surgery type non-specific	0.036	0	0.023
Surgery non-specific	0.038	-0.010	-0.03
Nonsurgical treatments (chemotherapy)			
Radiotherapy	0.078	0.090	0.104
Chemotherapy with toxicity or nausea/vomiting		-0.026	
Hormonal	0.077	0.074	0.074
Treatment non-specific	0.083	0.087	0.078
Time period (under 1 year)			
Over 1 year	0.1	0.038	0.058
Time non-specific	0.053	0.006	0.045
Whose values (community sample)			
Clinician	0.164	0.179	0.130
Patient's own health	0.171	0.209	0.162
Patient's scenario	0.085	0.084	0.077
Valuation method (standard gamble)			
VAS worst-best	-0.194	-0.187	NA
VAS dead-full	-0.205	-0.181	NA
EQ-5D	-0.215	-0.168	-0.112
TTO top not full health	0.074	0.099	NA
TTO different anchor	-0.014	0.008	0.016
TTO top full health	-0.157	-0.133	-0.110
Health Utility Index 3 (HUI3)	-0.248	-0.188	-0.132
Constant	0.725	0.663	0.648

Source: Peasgood et al. 2010.
Abbreviations: NA: Not applicable.

Table 6-7: Regression models for advanced breast cancer

Variables	Model 1	Model 2	Model 3
Treatment type (chemotherapy)			
Starting treatment	0.165	0.234	0.213
Hormonal	0.134	0.134	0.140
Radiotherapy	-0.105	-0.112	-0.153
Treatment non-specified	-0.015	0.017	0.016
Response to treatment (stable)			
Response	-0.085	0.097	0.088
Progression	-0.126	-0.205	-0.197
Terminal	-0.352	-0.390	-0.461
Response non-specified	-0.187	-0.267	-0.244
Side-effects (no side-effects mentioned)			

Variables	Model 1	Model 2	Model 3
Peripheral neuropathy	-0.085	-0.138	-0.142
Edema	-0.017	-0.011	-0.015
Febrile neuropathy		0.192	0.172
Sepsis	-0.228	-0.16	-0.192
Hypercalcemia	-0.628	-0.672	-0.856
Other side-effects	0.172	0.194	0.176
Whose values (community sample)			
Clinician	0.033	0.0000	0.016
Patient's own health	0.24	0.243	0.209
Patient's scenario	0.156	0.126	0.138
Valuation method (standard gamble)			
VAS worst-best	0.045	0.066	NA
VAS dead-full	-0.068	-0.060	NA
VAS rescaled dead-full	0.107	0.160	NA
EQ_5D	-0.0519	0.0173	0.0464
TTO top not full health	0.205	0.257	NA
TTO top full health	0.087	0.143	0.173
Constant	0.614	0.640	0.632

Source: Peasgood et al. 2010.
Abbreviations: NA: Not applicable.

Disutility weights for adverse occurrences due to tamoxifen treatment were derived from three sources (232, 249, 250). Adverse outcomes associated with tamoxifen intake include stroke, endometrial cancer, fractures, pulmonary embolism, hot flashes, vaginal bleeding, musculoskeletal disorders such as arthralgia, deep vein thrombosis (DVT) and pulmonary embolism (PE). However, after consultation with a Ghanaian clinical expert, adverse events included in both models were restricted to vaginal bleeding, musculoskeletal disorders (MSD) such as arthralgia, DVT and PE. Clinical experts determined the proportions of pre-and peri-menopausal women receiving tamoxifen who are likely to experience these types of adverse events.

Table 6-8 presents the disutility weights for each adverse event and their source. The utility weight assigned to a health state is a sum of the utility and disutility values associated with the state. Disutility values are expressed as a utility loss and so have a negative sign when used in the model.

Table 6-8: Disutility weights for adverse events included in the model

Adverse events	Disutility weight	Source
Vaginal bleeding	0.067	Mansel et al. 2007
Musculoskeletal disorders e.g. arthritis, arthralgia, myalgia	0.180	Fryback et al. 1993
Deep vein thrombosis	0.140	Cykert 2004
Pulmonary embolism	0.190	Cykert 2004

6.5.3 Death rates

Age-specific death rates for Ghanaian women were taken from the WHO database Global Cancer Observatory (GCO) (251). The most recent rates available are for 2015 (see Table 6-9 below).

Table 6-9: Annual age specific mortality rate for females in Ghana

Age	Annual Mortality rate
>1	0.039
1-4yr	0.005
5-9yrs	0.003
10-14yrs	0.002
15-19	0.002
20-24	0.003
25-29	0.003
30-34	0.004
35-39	0.005
40-44	0.006
45-49	0.007
50-54	0.009
55-59	0.012
60-64	0.02
65-69	0.033
70-74	0.057
75-79	0.099
80-84	0.173
85+	0.291

Source: WHO 2017.
Note: the age specific death rates were converted to correspond to the cycle length of each model.

6.5.4 Data for resource use and costs

The perspective of analysis chosen for the economic evaluation influences which resource use and costs are included in the evaluation. Costs are estimated by identifying resource use, measuring the items and valuing them by assigning unit cost to each resource/item. The

approaches to valuing resources (costing) within healthcare have been categorised broadly as top-down and bottom-up approaches (252-254). The top down approach involves the use of a defined metric to allocate a total budget to specific interventions/services such as breast cancer treatment. In this instance, the total budget could be the total health budget or total budget for cancer treatments in a hospital. The bottom-up approach assesses the amount of each resource used in providing a particular health service/intervention. This thesis used the bottom-up approach to cost breast cancer treatment.

Resource use for the health states for breast cancer and management of adverse events were sought from one clinical oncology expert in Ghana who agreed to participate in the study since no written treatment guideline/protocol exists for breast cancer treatment in Ghana. Unit costs were taken from the NHIS tariffs list for tertiary hospitals[26] and the medicines price list for the year 2016/17, and the KATH medicines and services pricing list. These prices were not inflated because they represented current price used for the year of evaluation[27]. The tariffs contain the unit costs of treatments in an aggregated form[28] and that of diagnostics in disaggregated form. The medicines price list also contains the unit cost per strength per quantity of a drug reimbursed under the NHIS.

In addition, costs incurred by patients and their families in accessing breast cancer treatment in Ghana was taken from an unpublished research by Gyau and Nonvignon (255), who estimated the economic burden per month for breast cancer patients seeking treatment in Ghana. In

[26] Breast cancer treatment is given in only two tertiary hospitals in the country.
[27] In cost analysis for economic evaluation, costs of resource use are inflated to present year currency value if costs were sourced from previous years. The accepted approach to adjusting prices incurred in different time periods for changing price levels (inflation) is to use the health component of the consumer price index. (8, 230). It is worth noting that, in Ghana there is no specific consumer price index for health commodities, hence this represents a challenge in making the appropriate adjustments.
[28] The NHIS has categorised services (treatments) under the Ghana Diagnostic Related Groupings (G-DRG), hence the tariff for each service rendered is related to the GDRG. Tariffs for a service was arrived at from consultation with the various stakeholders of health and using the average cost of resources/items (sourced from a survey of hodpitals) in the country.

addition to the direct medical costs, they estimated the direct non-medical and indirect costs to the patient. Direct medical costs included costs of treatment, laboratory investigations and consultation while direct non-medical costs included travel and food costs when seeking treatment. They estimated the indirect cost: time lost to seeking care, using the human capital approach. Therefore, this thesis used the direct non-medical and indirect costs borne by patients and families reported by Gyau and Nonvignon (255), in addition to the health system costs it estimated, to calculate the societal costs due to breast cancer treatment. Estimation of costs due to the treatment of early and advanced stage breast cancer for those who receive tamoxifen or not are presented in Chapters 7 and 8. All costs are estimated in 2017 prices.

6.6 Conclusion

This chapter presented the rationale for choosing tamoxifen for the treatment of HTBC in pre- and peri-menopausal women for the HTA appraisal. The existing economic evidence on tamoxifen was reviewed and its applicability to the Ghanaian context assessed. None of the economic evaluation studies were generalisable to the Ghanaian context for HTA, hence new data was identified for a new evaluation specific to Ghana. Economic information available in Ghana for the evaluation is limited. The only local data available were on resource use and costs. However, as no written treatment protocol for the treatment of breast cancer exists, one Ghanaian clinical expert who was willing to provide this information was relied on to estimate resource use, which could lead to over or under estimation of the cost of treating breast cancer. Costs of resources were derived from the NHIS and KATH pricing lists, which are reliable as they reflect what the funder pays for those services.

As data were lacking on the efficacy of tamoxifen and utility values for breast cancer health states in Ghana, international data could be identified and relied on. However, these need to be adequately transformed to be context-specific before they are suitable as inputs into a Ghanaian

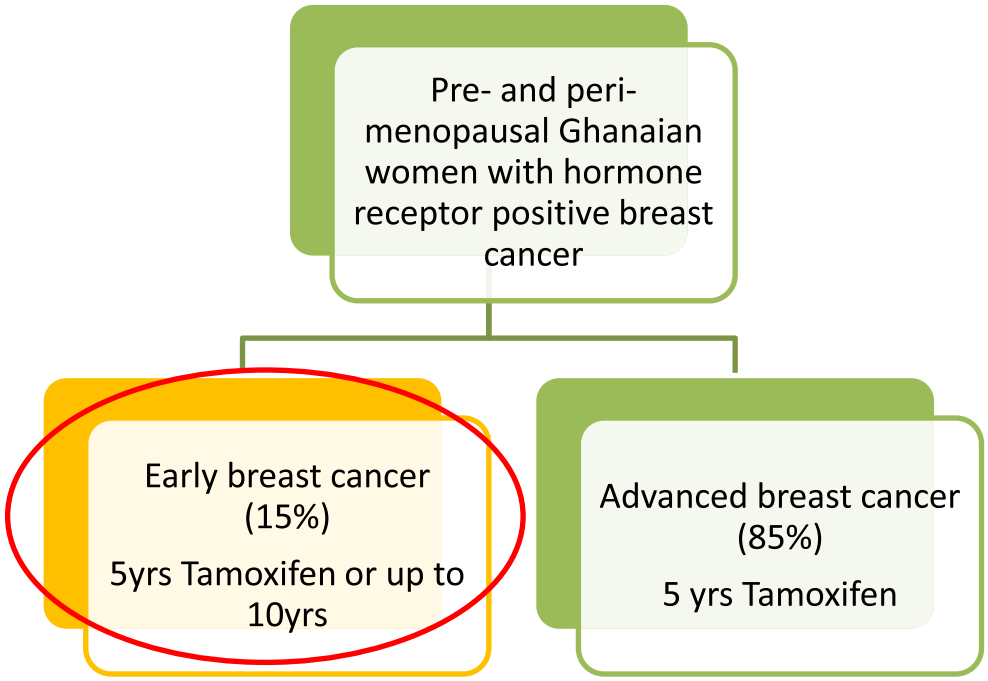
model evaluating the cost effectiveness of tamoxifen. Data were identified on the efficacy of tamoxifen only for early stage breast cancer while utility values identified were for both early and advanced stages of breast cancer.

The next chapter presents an economic evaluation of tamoxifen for the hormonal treatment of pre- and peri-menopausal Ghanaian women with early breast cancer, by transforming clinical efficacy and utility values and synthesising them with cost data to suit the Ghanaian context.

7 HTA IN GHANA: ECONOMIC EVALUATION OF TAMOXIFEN FOR THE HORMONAL TREATMENT OF EARLY BREAST CANCER AMONG PRE- AND PERI-MENOPAUSAL WOMEN

7.1 Introduction

This chapter presents an evaluation that addresses the question of whether tamoxifen is cost effective compared to no tamoxifen for the hormonal treatment of early breast cancer among pre- and peri-menopausal women in Ghana (Figure 7-1). It uses efficacy data from a meta-analysis of patient level data from 20 RCTs (213), a meta-regression of utility values (248) and resource use and costs identified in Chapter 6 to populate the model.



Note: The arm highlighted in a different colour and with an oval is the population of focus for the evaluation.

Figure 7-1: Proportions of Ghanaian pre- and peri-menopausal women with breast cancer according to stage of disease

The methodological approach used for the evaluation is presented in Section 7.2. This includes the structure, characteristics and assumptions of the model used. The section describes how the identified efficacy and utility data are transformed and used in the current evaluation that addresses whether tamoxifen is cost effective compared to no tamoxifen. The approach used in assessing the strength of the model input parameters in predicting the base case results are also presented under Section 7.2. Section 7.3 presents findings from the base case and sensitivity analysis. Section 7.4 discusses the findings using available literature. It elucidates the strengths and limitations of the methods and their implications for HTA in Ghana. The last section concludes the chapter by illuminating its main findings and implications for policy and future research.

7.2 Methods

The economic evaluation was conducted and reported according to the CHEERS checklist (see Appendix 6 Table 11-10 for the CHEERS statement). Table 7-1 presents the major characteristics of the model which are further explained in the sections below.

Table 7-1: Summary of model characteristics

Model characteristics	Inputs used in the base case model
Type of evaluation	Cost utility analysis
Perspective of analysis	Health system (payer)
Time horizon	15 years
Cycle length	Quarterly
Duration of treatment	5 years
Mean age of entry into model	49 years
Choice of health outcome	QALYs
Estimation of costs	Bottom- up approach
Date of resource estimation and unit costs	2017
Discount rate	3%

7.2.1 Structure and characteristics of the model

A Markov model was chosen as the most appropriate model for the analysis for two main reasons. First, it is widely used in medical decision-making and most economic evaluation

studies for breast cancer treatment. Second, breast cancer is a long-term disease with individuals progressing from one state to another, hence the appropriateness of a state-transition model, which incorporates the passage of time. Of the state-transition models, a Markov model was chosen over discrete event simulation or microsimulation because of the inaccessibility of patient level clinical trial data to simulate the time spent in each state by the patient, and their subsequent impact on other states patient transition into. A decision tree was used to capture the type of treatment a patient is assigned to in the model. The model was developed in TreeAge Pro Software 2017 (TreeAge Software. Incorporated, USA).

The cycle length in the Markov model was three months. This was chosen because Ghanaian women with early breast cancer and those in remission attend follow-up visits every three months. It was therefore assumed that any change in a patient's health state would be identified at those visits, as well as associated costs. All patients entered the model at age 49, the mean age at diagnosis of breast cancer incidence in Ghana. Heterogeneity due to age distribution of patients could not be accounted for in this model due to the clinical efficacy data available for use in this model, which are not reported by age. Therefore, the evaluation presented for this study is for a cohort of Ghanaian women aged 49 years. A subgroup analysis was conducted to account for the differences in the two age groups (<45 years and 45 to 54 years).

Patients are assumed to experience the same transition probabilities, health outcomes and resource use as they move through the model. A time horizon of 15 years was chosen for the model to be in line with life expectancy of the Ghanaian female population, 64 years. However, a sensitivity analysis was conducted to explore the impact of a longer time horizon. The effectiveness of tamoxifen was measured in QALYs gained for the base case analysis and in Life Years Saved and DALYs averted in a sensitivity analysis.

The analysis was conducted from the payer (NHIS) perspective. However, the societal perspective was included in a sensitivity analysis to evaluate the cost to the society, as patients and family incur costs due to seeking care (such as transportation) that are not reimbursed under the NHIS. The societal perspective in this study considers only the costs to the health system, NHIS patients and family. The ICER was calculated using the formula in Equation 2.

$$ICER = \frac{Costs\ of\ tamoxifen - Costs\ of\ no\ tamoxifen}{Effectiveness\ of\ tamoxifen - Effectiveness\ of\ no\ tamoxifen}$$ Equation 2

The model was designed to have four health states as shown in Figure 7-2. The model was developed in TreeAge software. Model structure used in the software is shown in Figure 7-3.

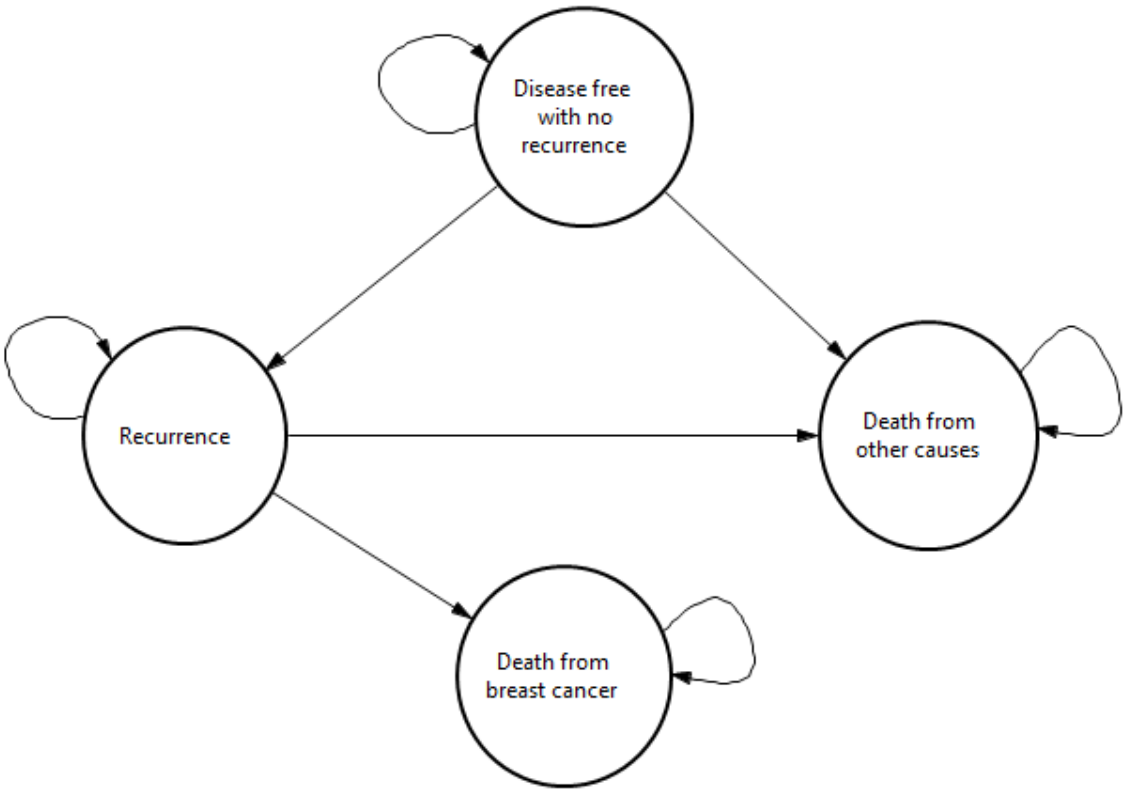
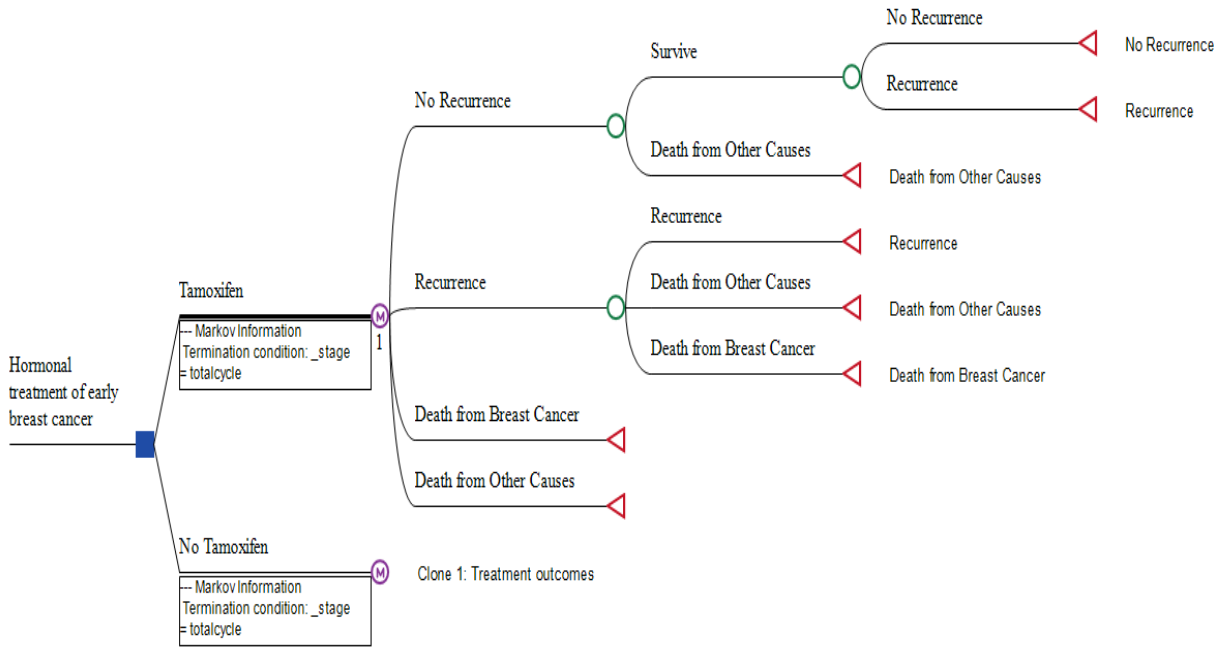


Figure 7-2: Markov transition states



Note: The model was created in TreeAge software; hence, this diagram presents the model structure as used in the software.

Figure 7-3: Economic model for the adjuvant treatment of early breast cancer in pre- and peri-menopausal women

Two additional health states were considered (with inputs from the review conducted and natural history of breast cancer) but excluded because of the following reasons:

1. The most appropriate efficacy data available for early breast cancer in pre-and peri-menopausal women could not comprehensively populate a six health state model that is described in Table 7-2.
2. The lack of data to derive transition probabilities for the excluded health states (see section 7.2.3. for a detailed description of the data).

Table 7-2: Description of the health states for breast cancer

Health state	Description
Disease-free with no recurrence	Patients on endocrine therapy or not, who do not have any new cancer occurrence or recurrence, with or without adverse events from endocrine therapy
Contralateral breast cancer	Patients on endocrine therapy or not, who have developed a new cancer in the opposite breast, with or without adverse events from endocrine therapy

Health state	Description
Loco-regional recurrence	Patients on endocrine therapy or not, who have developed a recurrence of cancer on the ipsilateral chest wall of the initial cancer with or without involvement of the regional lymph nodes (ipsilateral axillary or supraclavicular, infraclavicular, internal mammary), with or without adverse events from the endocrine therapy
Distant recurrence	Patients on endocrine therapy or not, who have developed cancers/tumours in all areas other than loco-regional recurrence and contralateral breast cancer, with or without adverse events from endocrine therapy
Death from other causes	Patients who die from causes other than breast cancer
Death from breast cancer	Patients who die because of the breast cancer

Table 7-3 presents the transitions that are possible in the model. Due to this limitation, a sensitivity analysis was conducted to test the structural uncertainty of the model under section 7.2.5**.**

Table 7-3: Transitions in the model

Health states	Transitions	Source of data
Disease-free with no recurrence		
	Remain in disease-free state	EBCTCG 2011
	Recurrence state	EBCTCG 2011
	Death from other causes	Ghana life tables
Recurrence state		
	Remain in recurrence state	EBCTCG 2011
	Death from other causes	Ghana life tables
	Death from breast cancer	EBCTCG 2011
Death from other causes	Absorbing state	Ghana life tables
Death from breast cancer	Absorbing state	EBCTCG 2011

Abbreviations: EBCTCG: Early Breast Cancer Trialists' Collaborative Group.

7.2.2 Additional assumptions used in the early breast cancer model

1. It was assumed that tamoxifen was administered for a period of five years, but has benefits lasting beyond five years as demonstrated in clinical trials (213). Five years of tamoxifen therapy was chosen as the base case model instead of 10 years of therapy to be consistent with other studies conducted in this area. In addition, it was deemed appropriate to present the cost effectiveness of tamoxifen taken for a minimum period of time to give decision makers an idea of the possible gains in QALYs even when it is taken for the minimum recommended duration of therapy. Lastly, the majority of breast

cancer survivors in Ghana die within the five years of therapy. It is also anticipated that more than 60% of women will not continue to take tamoxifen for up to ten years, thus its intended effect will not be achieved. Noncompliance of tamoxifen intake has been reported among Nigerian and South African women (256, 257). Therefore, five years tamoxifen therapy was deemed as modest and realistic. The effect of noncompliance to tamoxifen on the calculated ICER was assessed in this study. Non-compliance rate for tamoxifen treatment was not included in the base case evaluation because it was assumed as insignificant as patients who report to the hospital for treatment get enrolled under the NHIS if they are not upon diagnosis, hence removal of financial barrier to access. In addition, majority of patients diagnosed of breast cancer like any other cancer, see it as 'life threatening' condition hence seek and are compliant to treatment (expert opinion).

2. Adverse events were assumed to only occur during the period of hormonal treatment. This reflects what is reported in clinical trials where the adverse events are recorded and reported for only the years of ongoing tamoxifen treatment (213-215, 258). The economic evaluation studies reviewed also only considered adverse events during the period when patients were taking tamoxifen.
3. It was assumed that 10% of patients will experience vaginal bleeding, 24% musculoskeletal disorders, 1% pulmonary embolism and 1% deep vein thrombosis as adverse events due to tamoxifen (proportions provided by Ghanaian clinical expert)[29]. It was further assumed that patients could experience all the adverse events once during the entire period of tamoxifen therapy, except for musculoskeletal disorders. Therefore, the respective costs and disutilities associated with the adverse events were allocated to a patient at the beginning of the model when they enter the disease-free with no

[29] Only these adverse events were considered for the current model through consultation with expert.

recurrence state. For the 24% of all patients taking tamoxifen who experienced musculoskeletal disorders, the associated costs and disutilities were assumed to continue throughout the entire period they were taking tamoxifen (based on input from a clinical expert). In line with the Ghana tamoxifen treatment protocol, patients were assumed to continue taking tamoxifen in the case of these adverse events.

4. Mortality due to breast cancer in the Ghanaian population was assumed to be the same as reported in the efficacy data. This was chosen because of the unavailability of a Ghanaian breast cancer database or study to provide estimates. Although breast cancer mortality rates have been estimated for Ghana by the GCO of the WHO, these were not used. These estimates were based on the national incidence estimates that modelled survival using frequency data from all cancers and data from countries with similar characteristics. Therefore, the WHO advises that caution be exercised because of the low quality of data from which these estimates were derived (251).
5. Mortality due to other causes were also assumed to be the same as the age specific mortality rates in Ghana. It was further assumed that female mortality due to breast cancer was negligible (0.0001) (251) compared to overall mortality rates in the country (0.04) (259), hence it was not deducted from the overall rate.
6. It was assumed that patients who moved from one state to another in this model discontinued tamoxifen for the first three months while they received other treatment(s). Tamoxifen treatment was assumed to continue thereafter. This is in accordance with current treatment practices in the Ghana health system.

7.2.3 Model inputs

This section presents the transformation of data identified in Chapter 6 for inputs into the current model.

Efficacy of tamoxifen (transition probabilities)

As reported in Chapter 6, data on the efficacy of tamoxifen for the adjuvant treatment of early breast cancer in pre-and peri-menopausal women was obtained from the results of a meta-analysis conducted by the EBCTCG (213). They reported the recurrence rates of breast cancer were reduced throughout the first 10 years when tamoxifen was taken for 5 years compared to no tamoxifen intake for ER + and PR+ breast cancers. This reduction was higher in the first four years of intake (relative ratio (RR) = 0.53), followed by five-nine years (RR=0.68). The relative ratio was higher after year nine: 0.97 during years 10-14. The study also reported a decrease in breast cancer mortality throughout the first 15 years. Tamoxifen had slight or no effect on the breast cancer recurrence or mortality rates for ER– breast cancers.

The EBCTCG stratified their analysis by age of entry (<45, 45-54, 55-69, and ≥70 years), oestrogen receptor (ER) status, nodal status and trial. The endpoints for the meta-analysis were time to recurrence (defined as dates of first contralateral breast cancer, loco-regional recurrence, and distant recurrence), breast cancer mortality and death from other causes. The EBCTCG also presented time to contralateral breast cancer and other types of cancer as secondary endpoints. Recurrence and death rate ratios were derived from log-rank analyses by allocated treatment.

The proportions of patients who experienced the events of interest were also presented in supplementary material in four different year periods, 0-4, 5-9, 10-14 and 15+ years, for each treatment arm, allowing transition probabilities to be estimated for the age group of interest for this model. Table 7-4 presents a comparison of the characteristics of population in the meta-analysis study and that of the Ghanaian women with early breast cancer expected to take tamoxifen.

Table 7-4: Comparison between the targeted Ghanaian population and those from the meta-analysis

Characteristics	Ghanaian population	EBCTCG 2011
Age	Mean age at diagnosis - 49 years	≤55years
Stage of breast cancer	Stage I and II	Stage I and II
Hormone receptor status	Hormone receptor positive	Hormone receptor positive
Prior test	Hormone receptor status Histology to confirm cancer	For some studies hormone receptor status and histology to confirm cancer was conducted
Prior treatment	Lumpectomy Radiation	Breast conserving surgery Radiation and/or chemotherapy
Duration of tamoxifen intake	5 years	Mean duration of 5years
Dose of tamoxifen	20mg daily	20mg/30mg/40mg daily
Country	Ghana	Meta-analysis of trials carried out around the world

Abbreviations: EBCTCG: Early Breast Cancer Trialists' Collaborative Group.

Women younger than 45 and those aged between 45 and 55 were categorised as pre-and peri-menopausal. This assumption also allowed the data to capture the mean age of incidence of breast cancer in Ghanaian women. To estimate the probabilities, the proportions for each event for the two age groups presented in the article were summed. Probabilities were estimated from the available data. To account for the quarterly model cycle length, the annual probability needed to be converted to probability of the event occurring per quarter. However, probabilities cannot be merely divided by four since mathematically they do not bear the properties/function of divisibility. Therefore, to estimate the quarterly probability of transitioning from one state to the other probabilities were transformed to instantaneous rates (260-262) using the formulae presented in Equation 3. This rate is divided by four to obtain the rate per quarter, then the estimated rate per quarter was converted back to a probability per quarter using the formulae presented in Equation 4[30].

$$r = -\frac{1}{t}\ln(1-p) \qquad \text{Equation 3}$$

[30] For example, an annual probability of recurrence of 0.0407, when converted to rate will give 0.0416 per year. This will be divided by four to get 0.0104 per quarter. Therefore, the probability of recurrence per quarter will be 0.0103.

$$p = 1 - exp^{-rt}$$ Equation 4

Where p is the probability, r is the rate and t is the unit of time.

Table 7-5 presents the probabilities per quarter for the time periods used in the model. Age specific death rates for Ghanaian women in 2015 were used as the probability of dying from other causes (i.e. death without recurrence).

Table 7-5: Transition probabilities used for the model

Endpoints/Health states	Probabilities				Source of data
	0 – 4 years	5 – 9 years	10 – 14 years	15+ years	
Tamoxifen arm					
All recurrences	0.010340	0.007021	0.004910	0.003474	EBCTCG 2011
Contralateral breast cancer*	0.019812	0.036038	0.083186	0.063486	EBCTCG 2011
Loco-regional and distant recurrence*	0.473360	0.392117	0.263973	0.306902	EBCTCG 2011
Death without recurrence	Age specific death rate for Ghana				
Death with recurrence	0.054318	0.054318	0.054318	0.054318	EBCTCG 2011
No tamoxifen arm					
All recurrences	0.016320	0.008448	0.005346	0.004736	EBCTCG 2011
Contralateral breast cancer*	0.026931	0.044735	0.076527	0.071907	EBCTCG 2011
Loco-regional and distant recurrence*	0.414340	0.360464	0.277343	0.287258	EBCTCG 2011
Death without recurrence	Age specific death rate for Ghana				WHO 2017
Death with recurrence	0.068494	0.068494	0.068494	0.068494	EBCTCG 2011

Probabilities presented in this table have been calculated as 3-monthly according to model cycle.
*Used in a sensitivity analysis only.

Utilities and disutilities

Utility values for all health states were derived from the coefficients estimated by Peasgood et al. (248) [31]. This study adopted a standard gamble method of elicitation of utility values using a community sample for the baseline estimate. The remaining variables were arrived at in consultation with a clinical expert in Ghana who advised on what is likely to happen in each health state. For example, it was assumed that an individual with contralateral breast cancer

[31] Model 2 is preferred by the authors because it has a substantially larger sample size. It was weighted by the sample size using all available utility values.

will undergo breast conservation surgery, receive radiotherapy, and survive less than one year post-diagnosis.

In addition, for any health state defined as a combination of two or more states, the utility weight was computed by adding their utility weight values weighted by the proportions of Ghanaian women who are likely to be in each state at a particular point in time. It was also assumed that women who progress from any of the health states to a distant metastatic state would either remain stable or progress on treatment. Thus, the response to treatment variable was weighted by the proportions of Ghanaian women likely to progress or remain stable to treatment in the distant metastatic state.

Table 7-6 presents the utility weight values for each health state for the tamoxifen arm to be used in the early breast cancer model and how they were derived. Patients in the no tamoxifen arm did not benefit from the additional utilities derived from tamoxifen intake. Utilities per health state was derived under the assumption that they are additive and the impact of tamoxifen is independent to other factors (263). The utility weights derived for breast cancer health states could not be compared to the health state utility of a healthy person in Ghana as no studies have reported this, to the best of my knowledge.

Table 7-6: Utility weight values derived for the health state in early breast cancer

Health state	Variables included[a]	Utility weights[a]
Disease-free with no recurrence		
	Constant (baseline)	0.633
	Community value	0.000
	Standard gamble	0.000
	Breast conserving surgery	0.000
	Radiotherapy	0.090
	Hormonal therapy	0.074
	Time period over one year	0.038
	All variables for the state	**0.865**[b]
Contralateral breast cancer		
	Constant (baseline)	0.633
	Community value	0.000
	Standard gamble	0.000
	Breast conserving surgery	0.000
	Radiotherapy	0.090
	Hormonal therapy	0.074
	Time period under one year	0.000
	All variables for the state	**0.827**[b]
Loco-regional recurrence		
	Constant (baseline)	0.633
	Community value	0.000
	Standard gamble	0.000
	Breast conserving surgery	0.000
	Radiotherapy	0.090
	Hormonal therapy	0.074
	Chemotherapy	-0.026
	Time period under one year	0.000
	All variables for the state	**0.801**[b]
Distant recurrence		
	Constant (baseline)	0.640
	Community value	0.000
	Standard gamble	0.000
	Stable on treatment (0.3)	0.000
	Progress on treatment (0.7)	-0.205
	Side-effects	0.000
	Hormonal therapy	0.134
	Chemotherapy	0.000
	All variables for the state	**0.631**[b]
Loco-regional and distant recurrence		
	All variables for the states	**0.665**[c]
All recurrences (contralateral, loco-regional and distant)		
	All variables for the states	**0.675**[c]

a. Variables and their corresponding utility weight values are taken from the meta-regression analysis by Peasgood et al. (248) (see Table 7 for details). The variables assigned to each state were derived with inputs from a Ghanaian clinical expert.

b. The utility weight value for each state was estimated by summing the values for all the variables under it.

c. The utility weight value was derived by summing the utility value for each state, weighted by the proportion of Ghanaian women likely to be in those states. For the loco-regional and distant recurrence state, a proportion of 0.2 and 0.8 respectively were used. For all recurrences, a proportion of 0.07,0.18 and 0.75 for contralateral, loco-regional and distant were applied respectively.

Table 7-7 presents a comparison of the utility weights derived for the breast cancer states in the tamoxifen arm in this study and those used in the economic evaluation studies reviewed in Chapter 6, section 6.3. In contrast to this study, none of the five reviewed studies employed utility weights from a meta-regression analysis. While this study used values estimated from the general population (community), four reviewed studies estimated values from a patient population, and one from oncology nurses. The utility weight for disease-free state derived for this study is comparable to that of Shih et al. (225), but not the remaining studies that use higher values: about 0.100 difference. The utility weight for distant recurrence state derived for this study is also comparable to that used by Locker et al. (236). The utility weights for the remaining health states compared to those used in this study are lower or higher as shown in Table 7-7. Shih et al. (225) had the lowest utility weights for all the health states.

Table 7-7: Comparison of utility weight values for health states in breast cancer

	Disease-free	Contralateral breast cancer	Loco-regional	Distant recurrence	Whose values
Current study/model	***0.865***	***0.827***	***0.801***	***0.631***	***Community***
Rocchi and Verma (2006)	0.940	0.775	0.816	0.724	Patient
Locker et al. (2007)	0.965	0.702	0.766	0.642	Patient
Mansel et al. (2007)	0.989	0.914	0.911	0.882	Patient
Karnon, Delea and Barghout (2008)	0.989	0.911	0.911	0.796	Patient
Shih et al. (2012)	0.860	0.468	0.468	0.370	Oncology nurses

Note: Only studies that reported utility weights for all the four states under consideration were included in this comparison.

As discussed in section 6.5.2 of Chapter 6, the utility weight of a health state is estimated as the sum of the utility weight gain and utility weight loss from the treatment, where utility loss has a negative value. For example, the utility weight for a patient with early breast cancer, in a disease-free state with no recurrence who is on hormonal therapy (tamoxifen), with vaginal bleeding as an adverse event will be 0.795 (i.e. 0.865-0.07 (the absolute reduction of the

disutility weight of vaginal bleeding)). All utility and disutility values were recalculated to suit the model cycle length.

Resource use and costs

The cost of each health state and adverse events includes the costs of diagnosis, physician visits and treatment. The cost of diagnosis includes physician visits, laboratory tests, diagnostic tests such as pathology tests, radiology examinations and others. The cost of treatment includes surgery, hospitalisation, laboratory investigation, radiotherapy and other medicines excluding hormonal therapy, where applicable. Administration of treatment such as chemotherapy and costs associated with the treatment of adverse events were included.

Screening of patients for endometrial cancer is not a standard practice in Ghana with reasons attributed to no recorded incidence of endometrial cancer due to tamoxifen intake (input from clinical expert). This is probably because that higher proportions of women who survive breast cancer are pre-menopausal, and pre-menopausal women have a lower probability of getting endometrial cancer (264).

All costs were estimated for a three-month period (model cycle length) and in Ghanaian cedis (GHC) 2017 prices. The total cost of each item under a health or adverse event state was estimated as the unit cost multiplied by the proportion of patients likely to incur those costs multiplied by the frequency of use. The total costs per health state were therefore estimated as a sum of all cost items under each state. Cost of tamoxifen and costs due to adverse events were not added to the cost of each health state. They were added to each state in the model as a reward on their own. All assumptions made in the estimation of costs of resource use were made with input from a Ghanaian clinical expert. Unit costs were derived from the NHIS tariffs and medicines list and the KATH pricing list.

Table 7-8 presents the derivation of costs due to disease-free with no recurrence state, which constituted only costs due to follow-up visits.

Table 7-8: Derivation of cost due to no recurrence state

Cost item	Proportion treated	Frequency of use	Unit cost (GHC (AUD))	Total cost (GHC (AUD))
Physician visit				
Follow-up visits	100	1	26.04 (7.55)	26.04 (7.55)
Total costs	-	-	-	26.04 (7.55)

Abbreviations: AUD: Australian dollars, GHC: Ghana cedis. Exchange rate: 1 GHC is equivalent to 0.29 AUD.

Costs of recurrence state was derived as a summation of costs due to contralateral breast cancer, loco-regional breast cancer and distant recurrence, weighted by the proportions of patients assumed to get each type of recurrence. It was assumed that a patient would need four physician visits during the period of detection of a recurrence and its diagnosis.

Table 7-9 presents the estimation of costs due to contralateral breast cancer. It includes costs of diagnosis, surgery to remove cancerous cells and physician visits. These costs are assumed to be incurred once (from diagnosis to end of treatment). Subsequent costs incurred are due to follow-up visits and are categorised as ongoing.

Table 7-9: Estimation of costs due to contralateral breast cancer

Cost item	Proportion treated	Frequency of use	Unit cost (GHC (AUD))	Total cost (GHC (AUD))
Diagnosis				
Physician visit	100	4	26.04 (7.55)	104.16 (30.21)
Diagnostic tests				
Mammogram	100	1	29.03 (8.42)	29.03 (8.42)
Biopsy	100	1	15.75 (4.57)	15.75 (4.57)
Pathology test	100	1	100.00 (29.00)	100.00 (29.00)
Full blood count (FBC)	100	4	11.74 (3.41)	46.96 (13.62)
Liver function test (LFTs)	100	4	16.81 (4.87)	67.24 (19.55)
Kidney function test	100	4	12.60 (3.65)	50.40 (14.62)
Chest x-ray	100	1	17.17 (4.98)	17.17 (4.98)
CT scan (brain, chest, abdomen)	0	1	185.17 (53.70)	0.00 (0.00)
Liver scan	0	1	27.63 (8.01)	0.00 (0.00)
MRI - any part of the body	0	1	195.43 (56.67)	0.00 (0.00)
Sub-total cost of diagnostics				164.60 (47.73)
Total cost of diagnosis				268.76 (77.94)
Surgery				
Lumpectomy	100	1	742.55 (212.34)	742.55 (212.34)
Radiotherapy/chemotherapy				
Radiotherapy	100	40	73.17 (21.22)	2,926.80 (848.77)
Chemotherapy	0	6	188.55 (54.68)	0.00 (0.00)
Physician visit				
Follow-up visit	100	1	26.04 (7.55)	26.04 (7.55)
Total cost - initial				***4,126.10 (1,196.57)***
Total costs - ongoing				***26.04 (7.55)***

Abbreviations: AUD: Australian dollars, GHC: Ghana cedis. Exchange rate 1 GHC is equivalent to 0.29 AUD.

Derivation of costs of loco-regional and distant recurrence are presented in Table 7-10. Cost of diagnosing breast cancer recurrence was estimated in the same way as estimated for the contralateral breast cancer state. Cost of treating loco-regional breast cancer, however, consists of costs of radiotherapy, chemotherapy and surgery. In addition, cost of hospitalisation for treatment of severe symptoms such as difficulty in breathing was included in the costs of distant recurrence. It was also assumed that all patients with loco-regional breast cancer would undergo surgery, while 70% of those with distant recurrence undergo neo-adjuvant surgery. The ongoing cost of distant recurrence includes costs due to hospitalisation.

Table 7-10 : Estimation of costs due to loco-regional and distant recurrence states

Cost item	Percentage treated	Frequency of use	Unit cost (GHC (AUD))	Total cost (GHC (AUD))
Loco-regional recurrence				
***Diagnosis**				
Total cost of diagnosis				268.76 (77.94)
Surgery				
Lumpectomy	100	1	742.55 (212.34)	742.55 (212.34)
Radiotherapy/chemotherapy				
Radiotherapy	100	40	73.17 (21.22)	2,926.80 (848.77)
Chemotherapy				
Adriamycin + Cyclophosphamide (AC)				
Minimum dose	95	4	188.55 (54.68	716.49 (207.78)
Maximum dose	5	6	188.55 (54.68	56.57 (16.41)
Sub-total	98			702.16 (203.63)
Cyclophosphamide + methotrexate + Fluorouracil (CMF)				
Minimum dose	95	4	189.65 (55.00)	720.67 (208.99)
Maximum dose	5	6	189.65 (55.00)	56.90 (16.50)
Sub-total	2			15.55 (4.51)
Total cost of chemotherapy	100			717.71 (208.14)
Physician visit				
Follow-up visit	100	1	26.04 (7.55)	26.04 (7.55)
Total cost - initial				***4,699.03 (1,362.72)***
Total cots - ongoing				***26.04 (7.55)***
Distant recurrence				
***Diagnosis**				
Total cost of diagnosis				268.76 (77.94)
Surgery				
Neo-adjuvant surgery	70	1	742.55 (212.34)	519.785
Radiotherapy/chemotherapy				
Radiotherapy	0	40	73.17(21.22)	0.00 (0.00)
Chemotherapy				
Adjuvant chemotherapy				
Adriamycin + Cyclophosphamide (AC)				
Minimum dose	90	4	188.55 (54.68	678.78 (196.85)
Maximum dose	10	6	188.55 (54.68	113.13 (32.81)
Sub-total	98			776.07 (225.06)
Cyclophosphamide + methotrexate + Fluorouracil (CMF)				
Minimum dose	90	4	189.65 (55.00)	678.78 (196.85)
Maximum dose	10	6	189.65 (55.00)	113.79 (33.00)
Sub-total	2			15.93 (4.62)
Total cost of adjuvant chemotherapy				792.00 (229.68)
Neo-adjuvant chemotherapy	5	0.05	15.93 (4.62)	39.60 (11.48)
Total cost of chemotherapy	100			831.60 (241.16)
Others				
Hospitalisation	95	2	544.42 (157.88)	1,034.40 (299.98)
Physician visit				
Follow-up visit	100	1	26.04 (7.55)	26.04 (7.55)
Total cost - initial				***2,697.76 (782.35)***
Total costs - ongoing				***1,060.44 (307.53)***

Abbreviations: AUD: Australian dollars, GHC: Ghana cedis. Exchange rate 1 GHC is equivalent to 0.29 AUD.
*Costs of diagnosis was estimated in the same manner for contralateral breast cancer as in Table 7-9.

Table 7-11 presents the final estimation of recurrence state costs as used in this model. With input from the clinical expert, all recurrences were summed up under the assumption that 7% of patients will have contralateral breast cancer, 18% loco-regional breast cancer, and 75% distant breast cancer. Therefore, to derive an estimate for the recurrence state, each type of recurrence was multiplied by the proportion of patients assumed to have it before summation, as shown in Table 7-11.

Table 7-11: Estimation of costs due to recurrence state (all types of recurrence)

Type of recurrence	Proportion	Initial (GHC (AUD))		Ongoing (GHC (AUD))	
		Base estimate	*Estimate for recurrence state	Base estimate	*Estimate for recurrence state
Contralateral breast cancer	0.07	4,126.10 (1,196.57)	288.83 (83.76)	26.04 (7.55)	1.82 (0.53)
Loco-regional recurrence	0.18	4,699.03 (1,362.72)	845.83 (245.29)	26.04 (7.55)	4.69 (1.36)
Distant recurrence	0.75	2,697.76 (782.35)	2,023.32 (586.76)	1,060.44 (307.53)	795.33 (230.65)
Total (All recurrences)			**3157.97 (915.81)**		**801.84 (232.53)**

*Derived by multiplying base estimate by the proportion of patients
Abbreviations: AUD: Australian dollars, GHC: Ghana cedis. Exchange rate 1 GHC is equivalent to 0.29 AUD.

Costs due to adverse events were estimated in a similar way to the health states. A summary of costs estimated for each health state and adverse events per quarter is provided in Table 7-12. The main cost drivers for all the health states (except for disease-free with no recurrence) was the cost of radiotherapy followed by the cost of lumpectomy and then the cost of chemotherapy.

Table 7-12: Estimated costs for health states, adverse events and hormonal drugs

Cost centre	Cost	
	Initial (GHC(AUD))	Ongoing (GHC (AUD))
Cost of tamoxifen	109.50 (31.76)	109.50 (31.76)
Disease-free with no recurrence	26.04 (7.55)	26.04 (7.55)
Contralateral breast cancer*	4,126.10 (1,196.57)	26.04 (7.55)
Loco-regional and distant recurrence*	3,098.01 (898.42)	853.56 (247.53)
Recurrence (all)	3,157.97 (915.81)	801.84 (232.53)
All adverse events	315.22 (91.41)	10.95 (3.18)

*Used in a sensitivity analysis only
Note: All costs presented are per quarter (3 months). Initial costs are those that are incurred at the beginning of the state; it is incurred once. Ongoing costs are incurred throughout the period of treatment.
Abbreviations: AUD: Australian dollars, GHC: Ghana cedis. Exchange rate 1 GHC is equivalent to 0.29 AUD.

Summary of translational issues

Table 7-13 provides a summary of each translational issue discussed above and their use in the economic model presented in section 7.3.

Table 7-13: Summary of translational issues addressed and their uses in the model

Issues addressed	Results to be used in the model	Cross reference	Results used in sensitivity analysis	Cross reference
Applicability of clinical efficacy data – comparison of intervention and patient characteristics between Ghanaian population and source of data used in the model.	Economic model is based on efficacy data of clinical trials with characteristics applicable to the Ghanaian population.	Section 7.2.3	None	Sections 7.2.5, 7.3.2
Targeted literature search for utility values and their transformation to the health states in the model	DFS – 0.865 Recurrence – 0.675	Section 7.2.3	Utility values from other economic evaluation studies Lower and upper values of 95% CI for utilities	Sections 7.2.5, 7.3.2
Literature review for disutilities due to adverse events of tamoxifen and expert advice on what to include, frequency and proportion of AE	VB – 0.07 MSD – 0.18 DVT – 0.14 PE – 0.19	Section 7.2.3	Proportions of patients with AEs were varied	Sections 7.2.5, 7.3.2

Abbreviations: AEs: adverse events, CI: confidence interval, DFS: disease-free state, DVT: deep vein thrombosis, MSD: musculoskeletal disorders, NA: not applicable, PE: pulmonary embolism, VB: vaginal bleeding.

7.2.4 Discounting

Costs and health benefits are discounted in economic evaluations. The rationale behind discounting is that individuals exhibit positive time preferences (77). Drummond and McGuire (77) put forward three arguments that underpin this rationale: 1) Future gains in outcomes should be discounted because the diminishing marginal utility of these outcomes is accompanied by an expectation that individuals will consume more in the future. 2) Future consumption opportunities may not be available due to unforeseen circumstances such as death or illness or change in preferences over time. 3) Individuals prefer to consume benefits in the present rather than the future.

However, there continues to be a debate on whether costs and health benefits be discounted at the same rate or using differential rates, with the former recommended by a number of guidelines and national funding agencies[32]. Those (266, 267) who have argued for differential discounting have done so on the basis that societal time preference for health benefits are not the same as those for monetary costs and benefits. They recommended using a higher discount rate for costs than that used for health benefits since the latter are consumed in the future.

Those who have argued for a common discount rate for costs and health benefits (265, 268) based their arguments on the lack of empirical evidence to support the notion that the real societal value of health increases over time. This argument and the recommendation of a global discount rate of 3% per annum has recently been supported (92). However, guidelines recommend conducting a sensitivity analysis to explore the effect of a reasonable range of discount rates on the ICER. Therefore, in this study, all costs and effects are discounted at 3% in the base case and a sensitivity analysis is conducted to test the strength of the ICER to changes in the discount rate (92, 95, 96, 265).

7.2.5 Sensitivity analysis

Sensitivity analysis is a method used to explore the nature of the uncertainties in a model by varying the input parameters to establish their impact on the model outputs (in this case, ICER). Types of sensitivity analysis used in the literature include univariate, multivariate, probabilistic, threshold analysis, scenario analysis and analysis of extremes. This study used univariate, multivariate, scenario analyses and PSA to assess the robustness of the base case result to changes in the model inputs, to validate the model and to understand which inputs were driving the ICER.

[32] Making Choices in Health: WHO guide to cost-effectiveness (94), The Gates Reference Case for Economic Evaluation (95), The International Decision Support Initiative (iDsi) Reference Case for Economic Evaluation (96), Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses; the First and Second Panel on Cost-effectiveness in Health and Medicine (92, 265), NICE UK

Results from cost effectiveness models are prone to bias due to uncertainties surrounding the source of data used to populate the model, assumptions underlying the model, model structure, generalising results of the experimental population to the population in clinical practice and methods used in synthesising all the available evidence to estimate an ICER (260). To expatiate, clinical trials which are the main source of efficacy data on a technology use a sample population which may not be representative of the general population due to sampling error and also cannot be generalised to the population under investigation due to differences in epidemiology and clinical practice guidelines. In addition, methodological approach used in synthesising data, and the choice of a model structure representative of the disease and clinical pathway of the condition under investigation also informs the costs and benefits included in the model, the estimated ICER and subsequently the decision made based on the ICER by the decision maker (260, 261). As a result, these uncertainties need characterising to provide the decision maker with the information on the extent to which they could be certain about the ICER being used as a basis for decision-making.

Univariate sensitivity analysis

Table 7-14 presents the ranges used in the univariate sensitivity analysis. Utility weights and transition probabilities were varied using confidence intervals derived from the base estimates. For the utility weights, variations were done using the lowest, average and highest utility weights reported in economic evaluation studies of on adjuvant treatment of early breast cancer with tamoxifen, in addition to their upper and lower bound 95% confidence interval values. In the absence of confidence intervals for costs, a 'plausible' arbitrary range was chosen to vary them in the univariate sensitivity analysis as suggested by Gray et al. (73).

The cost estimates were adjusted upward and downward by 50%. Fifty percent (50%) was chosen under the assumption that costs of treatment could increase by up to half due to inflation or could decrease by half due to a reduction in the costs of health technologies over time. This

was also in line with the value chosen by Rocchi and Verma (230) who also used 50% increase and reduction in the absence of confidence intervals for costs. The discount rate was varied between 0% and 10% to test the effect of no rate and a higher discount rate on the ICER. The model time horizon was also adjusted upward and downward by 50%. The proportion /frequency of adverse events were varied by using those reported in the ABCSG-12 (in premenopausal women) (269) and ATAC (in postmenopausal women) (270) trials.

Table 7-14: Parameter ranges of used in the univariate sensitivity analysis

Parameter	Base estimate	Range for sensitivity analysis	
		Lower bound	Upper bound
Costs			
Cost of tamoxifen	109.50	54.75	164.25
Cost of adverse events (initial)	315.22	157.61	472.83
Cost of adverse events (ongoing)	10.95	5.48	16.43
Cost of no recurrence state	26.04	13.02	39.06
Cost of recurrence state (initial)	3,157.97	1,578.98	4,736.95
Cost of recurrence state (ongoing)	801.84	400.92	1,202.76
Utilities			
Utility for tamoxifen no recurrence state (CI)	0.87	0.74	0.98
Utility for no tamoxifen no recurrence state (CI)	0.79	0.68	0.92
Utility for tamoxifen recurrence state (CI)	0.67	0.53	0.87
Utility for no tamoxifen recurrence state (CI)	0.56	0.44	0.70
Utility for tamoxifen no recurrence state (reviewed literature)	0.87	0.96	0.97
Utility for no tamoxifen no recurrence state (reviewed literature)	0.79	0.92	0.93
Utility for tamoxifen recurrence state (reviewed literature)	0.67	0.67	0.89
Utility for no tamoxifen recurrence state (reviewed literature)	0.56	0.70	0.75
***Transition probabilities**			
Probability of death from breast cancer – tamoxifen arm	0.0543	0.0623	0.0845
Probability of death from breast cancer – no tamoxifen arm	0.0684	0.0711	0.0910
Others			
Discount rate	0.03	0	5, 10
Start age	49	34.3	49
Time horizon	15	10.5	19.5
[!]Proportion/frequency of adverse events (ABCSG-12 trial)	0.24	NA	NA
[+]Proportion/frequency of adverse events (ATAC trial)	0.24	NA	NA

*Transition probabilities are presented in more than two decimal places unlike the other parameters. Univariate sensitivity analysis was not conducted on the remaining transition probabilities because they were not point estimates. Estimates were a range and in tabular form for the 15 years' time horizon.

! Proportions/frequency for each adverse events used in the sensitivity analysis as reported by the trial; vaginal bleeding and discharge = 2%, DVT = 0.8%, PE = 0.8%, MSD = 14%, fracture = 2% and endometrial cancer/hyperplasia = 6%.
+ Proportions/frequency for each adverse events used in the sensitivity analysis as reported by the trial; vaginal bleeding and discharge = 19.6%, DVT = 3.5%, PE = 1.7%, MSD = 61%, fracture = 3.7% and endometrial cancer/hyperplasia = 0.8%.

Multivariate sensitivity analysis

The utility loss and costs due to adverse events were varied simultaneously as follows: no utility loss and no costs due to adverse events, to assess the effect on the base case results.

Scenario analysis: Subgroup analysis

The reference group for this evaluation, pre-and peri-menopausal women, was assumed to be a combination of two age groups – women aged less than 45 years and those aged 45 to 54 years, based on the available data. Because this reference group may not truly reflect the exact age of pre-and peri-menopausal women in Ghana, a subgroup analysis was conducted to ascertain the differences in ICER between the younger cohort, which may better reflect a pre-menopausal Ghanaian woman, compared to the older cohort, some of whom may still be pre- or peri-menopausal. It is expected that these two groups of women will have different characteristics such as baseline risks and mortality rates. There was also a difference in the treatment effects of tamoxifen for women aged <45 years and those aged 45 to 54 years (213). Even though this difference was statistically insignificant, it was assumed that the cost effectiveness of the group average might vary between the subgroups. In addition, it would be informative for a decision maker to know how much it would cost to treat each group.

Scenario analysis: Societal perspective of analysis

Patients and families incur additional costs including direct non-medical and indirect costs through seeking care. Therefore, to account for this cost, the analysis was conducted from societal perspective in a sensitivity analysis. Patient and family costs as discussed in Chapter 6 were derived from a study by Gyau and Nonvignon (255). They reported the direct non-medical

cost per month as GHC 44.86 (AUD 13.01), and indirect cost per month as GHC 99.58 (AUD 28.88). Hence, to evaluate the cost effectiveness of tamoxifen for the adjuvant treatment of breast cancer from the societal perspective, it was assumed that patients and families would incur these costs in addition to the costs incurred by the health system.

Scenario analysis: Using the patented and current market price of tamoxifen

As mentioned in Chapter 6, tamoxifen is no longer patented; hence, its acquisition cost is lower than when it was first introduced on the market. A scenario analysis was conducted to examine the cost effectiveness of tamoxifen vis-à-vis its affordability in terms of government funding under the NHIS when it was first introduced on the market, as in developed countries.

In addition, the current market price of tamoxifen was used to estimate its cost effectiveness to examine the impact of the price fluctuations on the ICER and subsequent, funding decisions made by policy makers.

Scenario analysis: Using transition probability of postmenopausal women

The probability of pre-and peri-menopausal women transitioning from one health state to the other was also varied using the transition probabilities of postmenopausal women. This was done to ascertain if the rate at which postmenopausal women switch from one health state to the other (which is different from that observed among postmenopausal women) (213, 258) has an impact on the base ICER estimated.

Scenario analysis: Structural uncertainty

To test for the structural uncertainty of the model, a second model was built to incorporate the contralateral breast cancer state to create five health states[33] (Figure 7-4) in all; disease-free,

[33] This model was not chosen as the base model even though some data was available because the probability of recurrence from contralateral breast cancer and disease-free state were assumed same in the absence of a trial reporting the former. Therefore, it was assumed appropriate to classify all the three states as recurrences in the base model. In addition, this was not consistent with other literature reviewed where contralateral and loco-

contralateral breast cancer, recurrence (loco-regional and distant recurrences), death from other causes and death from breast cancer, as made possible by the available data.

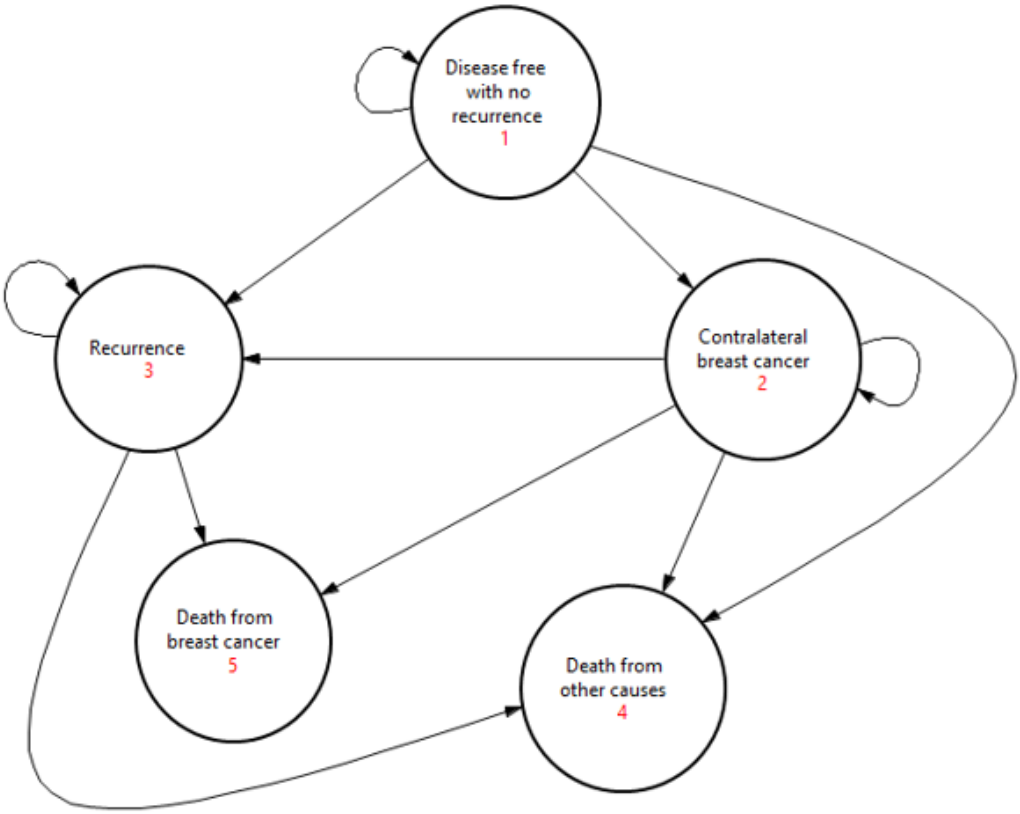


Figure 7-4: Model structure for sensitivity analysis (developed in TreeAge)

Scenario analysis: Change in duration of tamoxifen treatment (10 years)

Scenario analysis was conducted to evaluate the impact of taking tamoxifen for 10 years. Current breast cancer treatment guidelines (212, 221) recommend tamoxifen be taken for 5 years or 10 years since there is evidence of a decrease in recurrence rate and especially breast cancer mortality for that duration of tamoxifen therapy (214, 215). Presently in Ghana, some

regional were considered as one health state because they bear similar characteristics, unlike loco-regional and distant recurrence (which do not bear similar characteristics) against contralateral breast cancer.

survivors of early breast cancer beyond five years continue to take tamoxifen, with the longest period being 7 years (clinical expert opinion).

Data was obtained from clinical trials, in particular Davies et al.'s work based on the International ATLAS (Adjuvant Tamoxifen: Longer Against Shorter) breast cancer treatment trial (214) and a RCT by Gray et al., adjuvant Tamoxifen – to offer more? (aTTom) (215), that assessed the breast cancer recurrence and mortality between women who discontinued treatment after year five and those who continued for up to 10 years. To date, no trial has compared the differences in clinical endpoints between women who take tamoxifen for five years and those who take it for 10 years.

Therefore, to account for the extended effect of tamoxifen beyond five years compared to no tamoxifen, the effects of tamoxifen (transition probabilities) used for the baseline analysis in the periods after five years were weighted by the average percentage decrease in the rates of recurrences and breast cancer mortality reported for the tamoxifen arm in the ATLAS and aTTom trials[34] (214, 215). Other parameters in the model such as the cost of tamoxifen treatment, adverse events, utilities and disutilities were assumed to occur over the ten years of tamoxifen therapy.

Scenario analysis: Using life years saved as health out come

To assess the effect of quality of life on the base case ICER, life years saved was used as a health outcome measure in a sensitivity analysis.

Scenario analysis: Using DALYs as health outcome measure

In consonance with other economic evaluation studies conducted in Ghana and other developing countries, DALYs were used in addition to QALYs to describe the burden of

[34] 0.90% and 2.40% decrease in the rate of recurrence after year 5 and 10 respectively, compared to 5 years tamoxifen therapy. There was also a reported decrease in breast cancer mortality by 1.90% after five years and 2.25% after 10 years.

disease in a sensitivity analysis. As mentioned in Chapter 2, DALYs are estimated as the sum of YLL and YLD. YLL is a product of the number of deaths due to a condition and the life expectancy of the reference population at the time of death. YLD are also calculated as the product of the prevalence of the condition and the disability weight of that condition (87).

Disability weights for each breast cancer state were derived from the GBD study (2015 update) (271). In the GBD study, the health states for each health condition are assigned a disability weight that was derived from a survey of the general population of five countries[35] (272).

Using the breast cancer mortality rates estimated for this model, the proportions of patients who had died by the end of the model was used to estimate YLL, in accordance with the model assumptions. Age-specific life expectancy values for Ghanaian women with breast cancer were obtained from the world life expectancy website (273). The duration of a sequelae (that is the prevalence) for each health state in this model was derived in consultation with a clinical expert from Ghana and from the Australian Burden of Disease Study Working Paper 2 (274). The WHO YLL, YLD and DALY calculation templates were used to derive DALYs gained and DALYs averted. DALYs were discounted at 3%.

The number of DALYs averted per health state is estimated as the number of DALYs lost when no intervention is applied (in this case, for women in the no tamoxifen arm) minus the DALYs lost when an intervention is applied (in this case, in the tamoxifen arm).

Table 7-15 shows the DALYs per health state used in the sensitivity analysis. The difference between the two intervention arms is the DALYs averted due to tamoxifen for breast cancer recurrence. It is assumed that the same DALYs are averted when patients are in the disease-

[35] The names of the health states provided in the GBD are different from those used in this study. The descriptions of each health state were used only as a guide to assign the disability weight to the health states of the current study. For example, the health state 'cancer, diagnosis and primary therapy' in the GBD was assumed to be the same as the 'disease-free with no recurrence' state in this study.

free state irrespective of the treatment arms as per underlying principle of DALYs (i.e. disability is due to an illness). Appendix 6, Table 11-11 provides details of estimates used in deriving the DALYs gained and averted per health state.

Table 7-15: DALYs averted per health state

	DALYs averted	
Health state	**Tamoxifen arm**	**No tamoxifen arm**
Disease-free with no recurrence	0.87	0.87
Recurrence	0.30	0.00

Abbreviation: DALYs: Disability adjusted life years.

Scenario analysis: Noncompliance with tamoxifen treatment regimen

Noncompliance is defined in this context as patients not adhering to the recommended optimal treatment of tamoxifen for five years. This includes missing of dosages and discontinuation of medication for a particular period. In this scenario analysis, it was assumed that noncompliance with treatment regimen would lead to a reduction in the benefit of tamoxifen compared to the compliance rate of RCT (which is often assumed as 80%) (275).

To account for noncompliance, this study used a 32% reduction in the benefit of tamoxifen. The percentage of benefit reduction was derived from a study by McCowan et al. (276) where they reported 52% reduced time to recurrence for patients who missed some tamoxifen doses either for a shorter or longer period and those who discontinued treatment. Thus, the 32% reduction in tamoxifen benefit was estimated by accounting for 20% noncompliance already reported in the RCT. Based on noncompliance rates reported in the African setting (256, 257), a 16% and 5% reduction in benefit of tamoxifen was also explored.

The percentage reduction in the benefit of tamoxifen was modelled using the fraction of benefit where the percentage of reduction is used as a multiplier to weight the baseline hazard ratio (transition probability) (277). Under this approach a reduction in the benefit of tamoxifen does not change its costs.

Probabilistic sensitivity analysis (PSA)

A PSA was conducted to simultaneously vary uncertain parameters in the model for a specified range; distribution. Drummond and Sculpher (200) suggest that PSA is the preferred approach to characterising uncertainties surrounding an economic evaluation because it enables the structural assumptions within a model to be addressed through the generation of a distribution of the cost effectiveness/utility ratio from specified ranges of key parameters simultaneously. In a PSA, uncertain parameters are characterised using prior distributions, which may be assumed as parametric when the shape and scale parameters (alpha and beta/lambda) are derived from the literature, or non-parametric if estimates are obtained from observational or patient level data. In this study, the alpha and beta/lambda parameters are derived from the reported means and standard errors in the literature (261, 278).

Monte Carlo simulation methods were used in the PSA to explore the uncertainty surrounding the base ICER estimated. In this method, a potential parameter value is bootstrapped from the distribution estimated from the alpha and beta/lambda values (278). The new set of values are used as new inputs for the model to recalculate the ICER. This process is repeated using different values drawn from the distributions each time (referred to as a simulation) until the new ICER being estimated becomes stable by visual verification. The uncertainty surrounding the ICER is thus characterised once the ICER becomes stable. The ICER estimated from the PSA constitutes the mean ICER across all the simulations conducted.

The uncertainty is shown by the spread of the data. The difference between the deterministic and PSA-estimated ICERs are determined by the type of distributions specified for the PSA. The closer the estimates for the two ICERs, the more appropriate the type of distributions used and vice versa. Therefore, it is important careful thought is given to the distributions selected for a particular parameter. PSA results are presented as a cost effectiveness acceptability curve

(CEAC) or as a scatter plot on the cost effectiveness plane (that is, the incremental cost effectiveness scatter plot).

In this thesis, for the early breast cancer model, it was assumed that uncertainty surrounding the model input parameters could be described using the parametric distributions defined in Table 7-16. The justifications for each choice are presented in Table 7-16. Based on the means and standard errors, the estimates for the beta distribution were fitted using the method of moment approach. For the cost parameters, the standard error was assumed to be equal to one-half of the mean value estimated (due to limited information on the former, as reported in the literature (261)).

Table 7-16 : Parametric distributions used for PSA in the early breast cancer model

Type of parameter	Distribution	Justification	Alpha	Beta/ lambda
Transition probabilities	Beta	Parameters bounded by zero and 1	$\frac{mean^2 \times (1-mean)}{SE^2} - mean$	$alpha \times \frac{(1-mean)}{mean}$
Utilities	Beta			
Disutilities	-Gamma	Parameter is bounded by zero and infinity	$\frac{mean^2}{SE^2}$	$\frac{SE^2}{mean}$
Costs	Gamma	Parameters have zero as lower bound but have no upper bound		

Source: Briggs et al. 2003.
Abbreviations: SE: standard error.

Table 7-17 summarises the mean parameter values, assumed parametric distributions and the alpha and beta/lambda parameters estimated for the PSA.

Table 7-17: Model (early breast cancer) inputs for PSA

Variable	Value	Distribution	SE	α	β/λ
Transition probabilities					
Death due to breast cancer from recurrence – tamoxifen arm	0.05	Beta	0.001	4892.59	85180.04
Death due to breast cancer from recurrence – no tamoxifen arm	0.07	Beta	0.001	9750.40	132604.13
*Breast cancer recurrence from no recurrence – tamoxifen arm	0.01	Beta	0.00	1614.08	201460.52
*Breast cancer recurrence from no recurrence – tamoxifen arm	0.01	Beta	0.00	4047.27	349897.59
Utilities and disutilities					
No recurrence state – tamoxifen arm	0.87	Beta	0.08	14.55	2.27
Recurrence state – tamoxifen arm	0.67	Beta	0.13	8.42	4.06
No recurrence state – no tamoxifen arm	0.79	Beta	0.08	21.99	5.81
Recurrence state – no tamoxifen arm	0.56	Beta	0.12	9.53	7.61
Adverse events – initial*	-0.04	- Gamma	0.02	7.11	177.78
Adverse events – ongoing*	-0.01	- Gamma	0.01	4	400
Costs					
No recurrence state	26.04	Gamma	13.02	4	0.15
Recurrence state – initial	3157.97	Gamma	1578.98	4	0.00
Recurrence state - ongoing	801.84	Gamma	400.92	4	0.01
Tamoxifen	109.50	Gamma	54.75	4	0.04
Adverse events – initial	315.22	Gamma	157.61	4	0.01
Adverse events – ongoing	10.95	Gamma	5.48	4	0.37

Note: estimates used in the model were rounded up to five decimal places.
Abbreviations: SE: standard error, α: alpha, β: beta (estimated for beta distribution, λ: lambda (estimated for gamma distributions).
*Estimate was derived from the point estimate of both treatments for the 15-year period.
**Disutility.

7.3 Results

7.3.1 Base case deterministic results

Figure 7-5 presents the Markov trace for the model. In the tamoxifen arm, 85% of patients were alive at year five; 74% with no recurrence and 11% with recurrence, and 57% of patients were alive at the end of the 15-year time horizon; 51%, with no recurrence and 6% with recurrence. At the end of 15 years 26% had died from breast cancer, and the remainder died from other causes. In the no tamoxifen arm, 78% of patients were alive at year five; 65% with no recurrence and 13% with recurrence, however, by the end of the model time horizon, 46% of

patients were alive; 42%, with no recurrence and 4% with recurrence. At the end of 15 years, 37% had died from breast cancer, and the remainder from other causes.

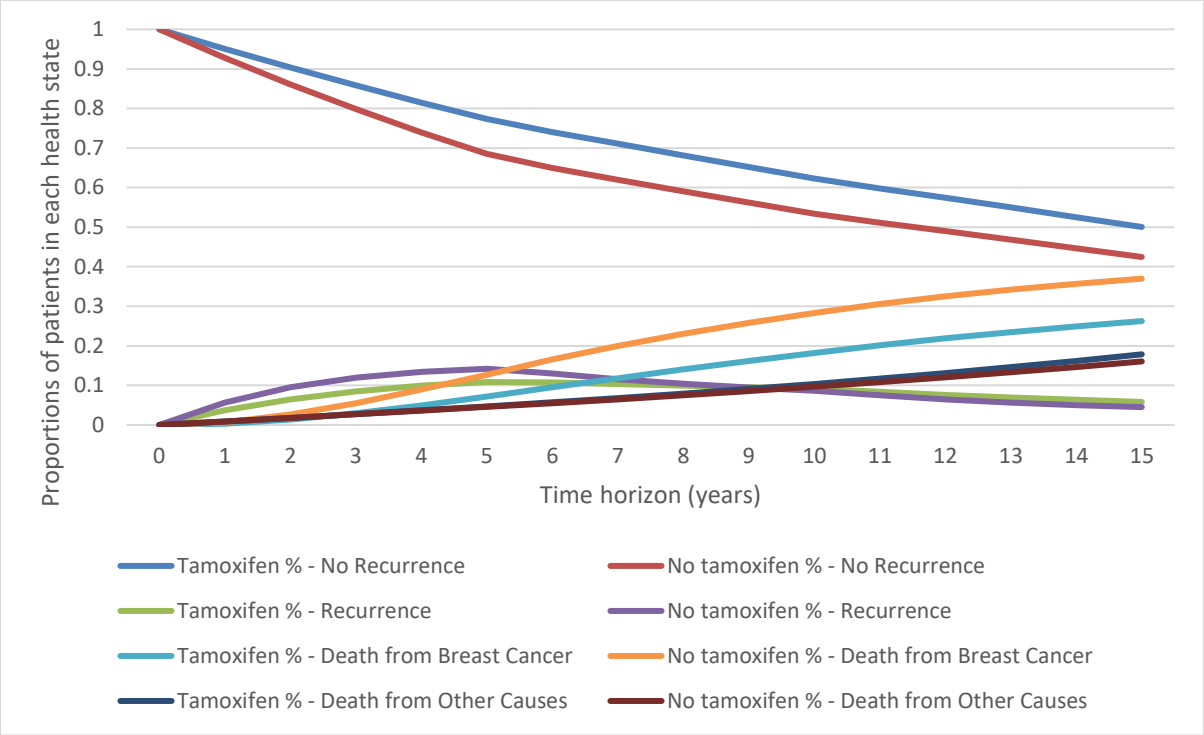


Figure 7-5: Markov trace for the model

To validate the model, the proportions of patients surviving for at least five years were compared to a recent Ghanaian study that used phone-calls and breast cancer registry of KATH to establish the survival rates of patients who has received treatment between 2009 to 2014 (279). They reported that 48.9% of patients had either died or had a recurrence irrespective of their HR status. This is similar to the percentage of patients who had either died or had a recurrence at the end of year five for both tamoxifen and no tamoxifen arm: 48%.

Another study reporting the survival of South African women with both node positive and node negative breast cancer, most (74%) of whom were on hormonal therapy, was used to further validate the model. In this retrospective study, Du Plessis and Apffelstaedt (257) reported an approximately 70% survival rate five years after the diagnosis of early breast cancer. It is expected that the overall survival of hormone receptor positive pre-and peri-menopausal

women in this model by year five (85%) will be higher than that observed in the study where only 74% were hormone receptor positive and thus received hormonal therapy.

Table 7-18 presents the estimated base case results: costs, health outcomes, and incremental cost effectiveness ratio. The average cost per patient in the base case was GHC 6,734 (AUD 1,953) and GHC 4,396 (AUD 1,275) for the tamoxifen and no tamoxifen arms respectively. The average QALY gained per patient was 8.31 for the tamoxifen arm and 6.93 for the no tamoxifen arm. The estimated incremental cost per patient for tamoxifen therapy was GHC 2,338 (AUD 678). A key driver of the incremental cost was the cost of tamoxifen accounted for 82% of costs. Costs of adverse events accounted for 16% of the incremental cost. Patients on tamoxifen therapy gained 1.38 QALYs; in the absence of adverse events, the QALYs gained were 1.44. Thus, adverse events contributed a 6% loss in QALYs. The ICER per patient for the base model was GHC 1,694 (AUD 491) per QALY gained.

Table 7-18: Incremental cost effectiveness ratio (ICER) for base case model

Treatment arm	Cost (GHC (AUD))	Incremental cost (GHC (AUD))	QALYs	QALYs gained	ICER (GHC (AUD))/QALYs gained
No tamoxifen	4,396 (1,275)		6.93		
Tamoxifen	6,734 (1,953)	2,338 (678)	8.31	1.38	1,694 (491)

Abbreviations: AUD: Australian dollars, GHC: Ghana cedis, ICER: incremental cost effectiveness ratio, QALY: quality adjusted life years.
Exchange rate 1 GHC is equivalent to 0.29 AUD.

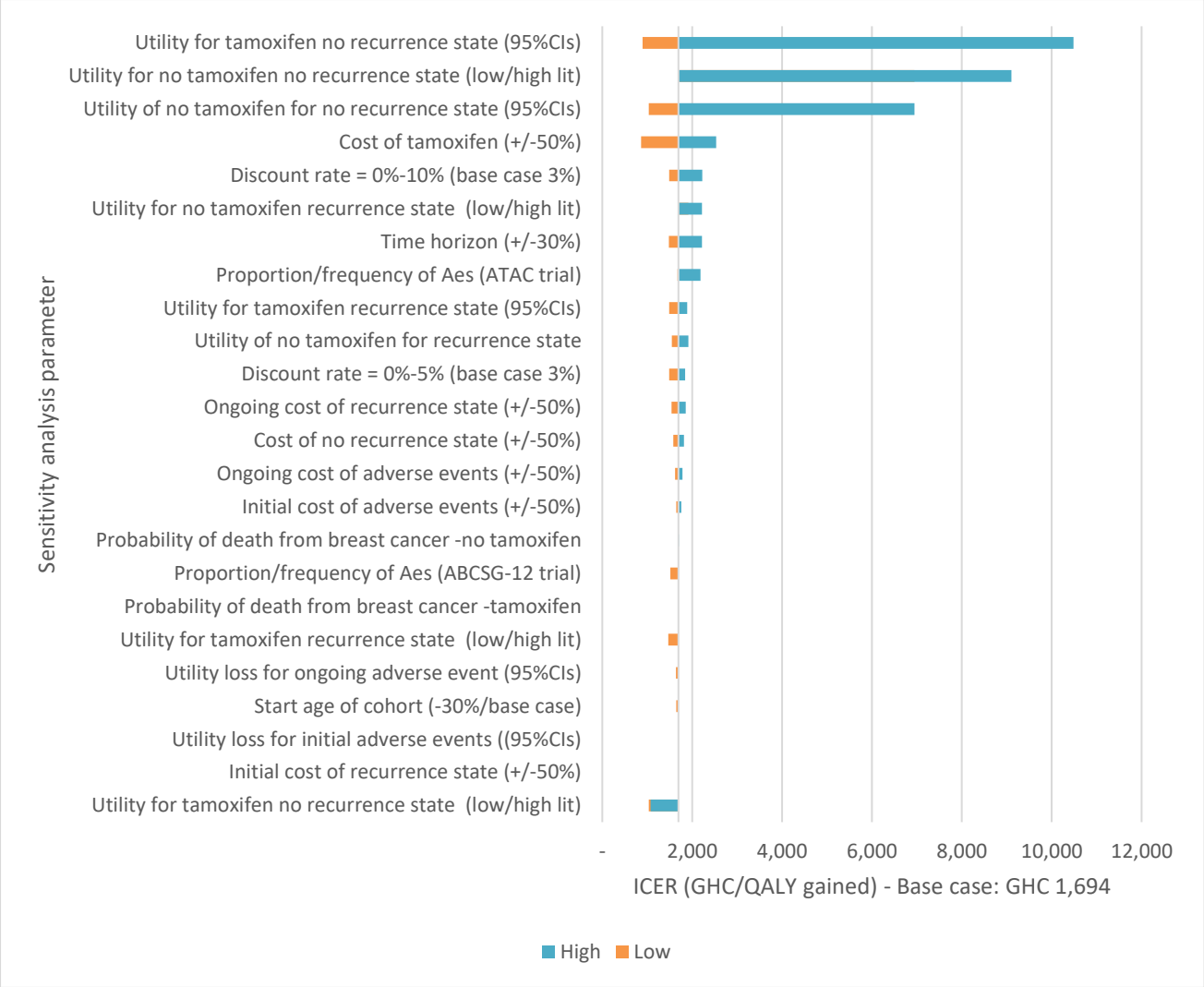
7.3.2 Sensitivity analysis

Univariate sensitivity, multivariate sensitivity, scenario analyses and PSA were conducted on the base case model to assess the robustness of the results to changes in the model inputs to validate the model and to understand which inputs were driving the ICER.

Univariate sensitivity analysis

Figure 7-6 and Table 7-19 present the results of the univariate sensitivity analysis for the base model with regard to a range of parameters. The ICER was most sensitive to variations in the utility weights used for the no recurrence state for the no tamoxifen arm, and the cost of tamoxifen. For example, using the average utility value derived from the literature reviewed for no recurrence state for the no tamoxifen arm increased the ICER by more than fourfold: GHC 8,993 (AUD2,608). Tamoxifen was dominated by the lower bound CI of utility value for no recurrence state for the no tamoxifen arm (ICER GHC 1,426 (AUD 413). A 50% increase in the cost of tamoxifen increases the ICER by almost half (49%): GHC 2,527 (AUD 733). Conversely, a 50% decrease in the costs of tamoxifen decreases the ICER by 49%; GHC 861 (AUD 250).

The ICER was sensitive to the time horizon of the model. A lifetime horizon increased the QALYs gained to 1.99; an increase of 0.61 QALYs compared to the base model. Removing adverse events in the model leads to an additional 0.06 QALYs gained and a minimal decrease (6%) in the ICER to GHC 1,624 (AUD 471). Assuming no costs due to adverse events decreased the ICER by 16%: GHC 557 (AUD 162). A 0% discount increased the QALYs gained to 1.73 (25% increase) and led to a corresponding decrease in the ICER to GHC 1,492 (AUD 433). A 10% discount rate decreased QALYs gained to 0.87 and had some considerable (31% increase) impact on the ICER: GHC 2,217 (AUD 643). The other parameters had minimal impact on the ICER as shown in Table 7-19.



Abbreviations: Aes: adverse events, lit: literature

Figure 7-6: Tornado diagram for univariate sensitivity analysis of individual parameters

Table 7-19: ICERs for univariate sensitivity analysis

Sensitivity analysis parameter	Incremental cost (GHC (AUD))	QALYs gained	ICER (GHC (AUD)) /QALY gained
**50% increase in cost of tamoxifen*	3,489 (1,012)	1.38	2,528 (733)
**50% decrease in cost of tamoxifen*	1,188 (344)	1.38	861 (250)
25% decrease in cost of tamoxifen	1,763 (511)	1.38	1,278 (370)
50% increase in cost of no recurrence state	2,174 (630)	1.38	1,575 (457)
50% decrease in cost of no recurrence state	2,502 (426)	1.38	1,813 (526)
50% increase in initial cost of adverse events	2,417 (701)	1.38	1,751 (508)
50% decrease in initial cost of adverse events	2,259 (655)	1.38	1,637 (475)
50% increase in ongoing cost of adverse events	2,451 (711)	1.38	1,776 (515)
50% decrease in ongoing cost of adverse events	2,226 (646)	1.38	1,613 (468)
50% increase in initial cost of recurrence	2,338 (678)	1.38	1,694 (491)
50% decrease in initial cost of recurrence	2,338 (678)	1.38	1,694 (491)
50% increase in ongoing cost of recurrence	2,120 (615)	1.38	1,537 (446)

Sensitivity analysis parameter	Incremental cost (GHC (AUD))	QALYs gained	ICER (GHC (AUD)) /QALY gained
50% decrease in ongoing cost of recurrence	2,556 (741)	1.38	1,852 (537)
30% increase in time horizon	2,455 (712)	1.66	1,474 (428)
30% decrease in time horizon	2,210 (641)	0.99	2,220 (644)
Lifetime (100% increase) time horizon	2,535 (735)	1.99	1,274 (370)
Start age of model entry 34.3 years	2,378 (690)	1.45	1,640 (476)
0% discount rate	2,582 (749)	1.73	1,492 (433)
5% discount rate	2,202 (639)	1.19	1,851 (537)
10% discount rate	1,929 (559)	0.87	2,217 (643)
Average utility values (in reviewed literature) for tamoxifen no recurrence state	2,338 (678)	2.26	1,035 (300)
**Average utility values (in reviewed literature) for no tamoxifen no recurrence state*	2,338 (678)	0.26	8,993 (2,608)
Average utility values (in reviewed literature) for tamoxifen recurrence state	2,338 (678)	1.47	1,591 (461)
Average utility values (in reviewed literature) for no tamoxifen recurrence state	2,338 (678)	1.19	1,965 (570)
Lowest utility value (in reviewed literature) for tamoxifen no recurrence state	2,338 (678)	2.17	1,078 (312)
Highest utility value (in reviewed literature) for tamoxifen no recurrence state	2,338 (678)	2.26	1,035 (300)
Lowest utility value (in reviewed literature) for tamoxifen recurrence state	2,338 (678)	1.38	1,694 (491)
Highest utility value (in reviewed literature) for tamoxifen recurrence state	2,338 (678)	1.59	1,471 (426)
**Lowest utility value (in reviewed literature) for no tamoxifen no recurrence state*	2,338 (678)	0.34	6,877 (1,994)
**Highest utility value (in reviewed literature) for no tamoxifen no recurrence state*	2,338 (678)	0.26	8,993 (2,608)
Lowest utility value (in reviewed literature) for no tamoxifen recurrence state	2,338 (678)	1.22	1,917 (556)
Highest utility value (in reviewed literature) for no tamoxifen recurrence state	2,338 (678)	1.05	2,227 (646)
**Lower bound 95% CI for utility value for tamoxifen no recurrence state	2,338 (678)	-1.64	-1,426 (413)
Higher bound 95% CI for utility value for tamoxifen no recurrence state	2,338 (678)	1.38	1,694 (491)
Lower bound 95% CI for utility value for no tamoxifen no recurrence state	2,338 (678)	2.25	1,039 (301)
**Higher bound 95% CI for utility value for no tamoxifen no recurrence state*	2,338 (678)	0.42	5,567 (1,614)
Lower bound 95% CI for utility value for tamoxifen recurrence state	2,338 (678)	1.24	1,886 (547)
Higher bound 95% CI for utility value for tamoxifen recurrence state	2,338 (678)	1.57	1,489 (432)
Lower bound 95% CI for utility value for no tamoxifen recurrence state	2,338 (678)	1.51	1,548 (449)
Higher bound 95% CI for utility value for no tamoxifen recurrence state	2,338 (678)	1.22	1,917 (556)
50% increase in utility loss due to adverse events	2,338 (678)	1.35	1,732 (502)
No utility loss due to adverse events	2,338 (678)	1.44	1,624(471)
No costs due to adverse events	1,956 (567)	1.38	1,417 (411)

Sensitivity analysis parameter	Incremental cost (GHC (AUD))	QALYs gained	ICER (GHC (AUD)) /QALY gained
Proportion/frequency of adverse events (ABCSG-12 trial)	2,216.53 (642.79)	1.38	1,611.62 (467,37)
Proportion/frequency of adverse events (ATAC trial)	2,663.09 (772.30)	1.38	1,936.31 (561.53)

Abbreviations: AUD: Australian dollars, GHC: Ghana cedis, CI: confidence interval, QALY: quality adjusted life years, ICER: incremental cost effectiveness ratio. Exchange rate: 1 GHC is equivalent to 0.29 AUD.
**Dominant
*ICER is most sensitive to parameter

Multivariate sensitivity analysis

The multivariate sensitivity analysis results are presented in Table 7-20. There was a minimal impact on the QALYs gained and the ICER: 1.44 QALYs and GHC 1,358 (AUD 394); 20% decrement, suggesting that adverse events are not a major driver of the ICER.

Table 7-20: ICERs for multivariate sensitivity analysis

Sensitivity analysis parameter	Incremental cost (GHC (AUD))	QALYs gained	ICER (GHC (AUD)) /QALY gained
Multivariate analysis			
No utility loss and no costs due to utility loss	1,956 (567)	1.44	1,358 (394)

Abbreviations: AUD: Australian dollars, GHC: Ghana cedis, QALY: quality adjusted life years, ICER: incremental cost effectiveness ratio. Exchange rate: 1 GHC is equivalent to 0.29 AUD.

Scenario analysis: subgroup analysis

Table 7-21 presents the results of ICER for the evaluation of tamoxifen for HTBC for the different age groups of pre-and peri-menopausal women. To treat a younger cohort with tamoxifen costs more as compared to an older one: GHC 2,480 (AUD 719) versus GHC 2,236 (AUD 648). However, the additional cost is offset by the QALYs gained because the younger cohort gained more QALYs than the older cohort: 1.57 versus 1.22 respectively. Therefore, the estimated ICER per patient was GHC 1,580 (AUD 458) for women less than 45 years of age and GHC 1,833 (AUD 531) for women aged 45 to 54 years — a 16% difference.

Table 7-21: ICER for subgroup analysis

Treatment arm	Cost (GHC (AUD))	Incremental cost (GHC (AUD))	QALYs	QALYs gained	ICER (GHC (AUD))/QALYs gained
<45 years					
No tamoxifen	4,299 (1,247)		6.58		
Tamoxifen	6,780 (1,966)	2,480 (719)	8.15	1.57	1,580 (458)
45 to 54 years					
No tamoxifen	4,446 (1,289)		7.21		
Tamoxifen	6,681 (1,938)	2,236 (648)	8.43	1.22	1,833 (531)

Abbreviations: AUD: Australian dollars, GHC: Ghana cedis, QALY: quality adjusted life years, ICER: incremental cost effectiveness ratio. Exchange rate: 1 GHC is equivalent to 0.29 AUD.

Scenario analysis: Societal perspective of analysis

Table 7-22 presents the ICER from the societal perspective. As anticipated, using a societal perspective led to additional costs incurred in both treatment arms; the incremental cost rose from GHC 2,338 (AUD 678) to GHC 2,466 (AUD 715). The ICER was GHC 1,787 (AUD 518). Hence including the costs incurred by patients and family into the evaluation results in a small additional incremental cost and ICER.

Table 7-22: ICER estimated from the societal perspective

Treatment arm	Cost (GHC (AUD))	Incremental cost (GHC (AUD))	QALYs	QALYs gained	ICER (GHC (AUD))/QALYs gained
No tamoxifen	12,097 (3,508)		6.93		
Tamoxifen	14,563 (4,223)	2,466 (715)	8.31	1.38	1,787 (518)

Abbreviations: AUD: Australian dollars, GHC: Ghana cedis, QALY: quality adjusted life years, ICER: incremental cost effectiveness ratio. Exchange rate: 1 GHC is equivalent to 0.29 AUD.

Scenario analysis: Using the patented and current market price of tamoxifen

The monthly cost of tamoxifen when it was first introduced on the market in the USA in 1977 was USD 44. To estimate the equivalent cost in 2017, the 1977 price was adjusted for health care inflation over the period. The monthly cost of tamoxifen would be USD 177.97 (equivalent to GHC 806 (AUD 234)) in the year 2017 assuming the drug was brought to the market in

2017[36]. Therefore, the ICER/QALY gained of tamoxifen as a patented drug was estimated as GHC 36,843 (AUD 10,684), which is significantly higher than the base ICER (Table 7-23). Using the current market price of tamoxifen also resulted in a 63% increase in the base ICER: GHC 2,768 (AUD 803) (Table 7-23) versus GHC 1,694 (AUD 491).

Table 7-23: ICER using the patented and current market price of tamoxifen

Sensitivity analysis parameter	Incremental cost (GHC (AUD))	QALYs gained	ICER (GHC (AUD)) /QALY gained
Patented price of tamoxifen	50,843 (14,744)	1.38	36,843 (10,684)
Current market price of tamoxifen	3,819 (1,108)	1.38	2,768 (803)

Abbreviations: AUD: Australian dollars, GHC: Ghana cedis, QALY: quality adjusted life years, ICER: incremental cost effectiveness ratio. Exchange rate: 1 GHC is equivalent to 0.29 AUD.

Using transition probability of postmenopausal women

Table 7-24 presents the ICER for this scenario analysis. Using the transition probabilities for older women (55 years or more) led to an increase in the QALYs gained of 1.83, and a minimal (33%) change in the ICER to GHC 1,339 (AUD 388). This suggests that treating postmenopausal women with tamoxifen would be cost effective compared to pre-menopausal women, due to the higher incidence of breast cancer recurrence and deaths in postmenopausal women.

Table 7-24: ICER estimated using transition probabilities for postmenopausal women

Sensitivity analysis parameter	Incremental cost (GHC (AUD))	QALYs gained	ICER (GHC (AUD)) /QALY gained
Scenario analysis			
Transition probabilities for older women ≥55	2,450 (710)	1.83	1,339 (388)

Abbreviations: AUD: Australian dollars, GHC: Ghana cedis, QALY: quality adjusted life years, ICER: incremental cost effectiveness ratio. Exchange rate: 1 GHC is equivalent to 0.29 AUD.

Scenario analysis: Structural uncertainty

Table 7-25 presents the ICER for this scenario analysis. The change in the structure of the model had only subtle impact on the ICER. The incremental cost decreased minimally (0.7%)

[36] The price of tamoxifen in 1977 (280) was adjusted to current price using the health CPI provided by the Bureau of Labour Statistics, Unites States Labour Department (281).

to GHC 2,323 (AUD 674) versus GHC 2,338 (AUD 678). The QALY gained was the same as the base case (1.38) and the ICER per patient was GHC 1,683 (AUD 488) — a 0.7% decrement. The most likely explanation for these results is that the probability of transitioning from contralateral breast cancer to a recurrence state is the same as that of a transition from a disease-free state to recurrence.

Table 7-25: ICER estimated from a five-state model that tests the structural uncertainty of the base case model

Sensitivity analysis parameter	Incremental cost (GHC (AUD))	QALYs gained	ICER (GHC (AUD)) /QALY gained
Scenario analysis			
Structural uncertainty	2,323 (674)	1.38	1,683 (488)

Abbreviations: AUD: Australian dollars, GHC: Ghana cedis, QALY: quality adjusted life years, ICER: incremental cost effectiveness ratio. Exchange rate: 1 GHC is equivalent to 0.29 AUD.

Scenario analysis: Change in duration of tamoxifen treatment (10 years)

Table 7-26 presents the ICER per QALYs gained when tamoxifen therapy was continued for 10 years. The incremental cost per treatment increased by 61% to GHC 3,758 (AUD 1,090). The increased ICER was not associated with an increase in the QALYs gained (1.38). This could be attributed to the observed difference between 5 years and 10 years tamoxifen therapy only after year ten. A longer time horizon did not result in higher QALYs gained compared to the 5 years tamoxifen therapy: 1.98 versus 1.99 (see Table 7-26 and Table 7-19 respectively). The continuous utility loss due to adverse events over the 10 years contributed to the decreased QALYs gained. In addition, the increased ICER could also be because of the unavailability of effectiveness data for 10 years tamoxifen therapy beyond year 15.

On the other hand, the incremental cost and subsequent increased ICER confirms the base case results and subsequent sensitivity analysis that, the cost of tamoxifen is a key driver of the ICER. The ICER per QALY gained for a ten-year tamoxifen therapy was GHC 2,723 (AUD 790), a 61% increase compared to the base case ICER.

Table 7-26: ICER for 10 years tamoxifen therapy

Treatment arm	Cost (GHC (AUD))	Incremental cost (GHC (AUD))	QALYs	QALYs gained	ICER (GHC (AUD)) /QALYs gained
15 years' time horizon					
No tamoxifen	4,396 (1,275)		6.93		
Tamoxifen	8,153 (2,365)	3,758 (1,090)	8.31	1.38	2,723 (790)
Lifetime horizon					
No tamoxifen	5,196 (1,507)		8.71		
Tamoxifen	9,156 (2,655)	3,960 (1,148)	10.69	1.98	2,000 (580)

Abbreviations: AUD: Australian dollars, GHC: Ghana cedis, QALY: quality adjusted life years, ICER: incremental cost effectiveness ratio. Exchange rate: 1 GHC is equivalent to 0.29 AUD.

Scenario analysis: Using life years saved as health outcome

Table 7-27 presents the estimated ICER using life years saved as health outcome compared to QALYs gained for tamoxifen in the base case. The average life years saved per patient was 9.78 for the tamoxifen arm and 9.10 for the no tamoxifen arm compared to the average QALY gained per patient, which was 8.31 for the tamoxifen arm and 6.93 for the no tamoxifen arm. Even though the average life years per patient for both arms were higher compared to the average QALYs per patient, the incremental benefit was higher when utility weights were applied to the model: 1.38 QALYs versus 0.68 life years. This indicates that the additional benefits seen with the QALY is due to the quality of life of patients and not merely the duration of life. It also implies that QALYs are a key driver of the estimated ICER. The ICER per patient was GHC 3,160 (AUD 916) per life years saved; — 86% increase in the base case result.

Table 7-27 : Comparison of ICERs using QALYs and Life Years Gained as health outcome

Treatment arm	Costs		Life years			QALYs		
	Cost (GHC (AUD)	Incremental cost (GHC (AUD))	LY	LYG	ICER (GHC (AUD))/ LYG	QALYs	QALYs gained	ICER (GHC (AUD)) /QALYs gained
No tamoxifen	4,396 (1,275)		9.10			6.93		
Tamoxifen	6,734 (1,953)	2,338 (678)	9.84	0.74	3,160 (916)	8.31	1.38	1,694 (491)

Abbreviations: AUD: Australian dollars, GHC: Ghana cedis, LY: life years, LYG: life years gained, QALY: quality adjusted life years, ICER: incremental cost effectiveness ratio.
Exchange rate: 1 GHC is equivalent to 0.29 AUD.

Scenario analysis: Using DALYs as health outcome

Table 7-28 presents the ICER per DALYs averted in treating pre-and peri-menopausal women with tamoxifen in the adjuvant setting for early breast cancer. The costs per treatment arm and the incremental costs are the same as the base case results. However, the DALYs averted for the no tamoxifen and tamoxifen arms were 6.98 and 8.00, respectively. Therefore, adjuvant treatment of pre-and peri-menopausal women with early breast cancer using tamoxifen leads to 1.05 additional DALYs averted per patient, which is less than the QALYs gained. The ICER per DALYs averted is GHC 2,227 (AUD 64) which is 31% higher than the ICER per QALY gained per patient in the base results (GHC 1,694 (AUD 491)). As previously discussed, QALYs and DALYs are different measures of quantifying health outcomes which use different methodological approaches and are therefore not comparable.

Table 7-28: Incremental cost effectiveness ratio (ICER) using DALYs as health outcome

Treatment arm	Cost (GHC (AUD))	Incremental cost (GHC (AUD))	DALYs averted	Incremental DALYs averted	ICER (GHC (AUD))/DALYs averted
No tamoxifen	4,3956 (1,275)		6.95		
Tamoxifen	6,734 (1,953)	2,338 (678)	8.00	1.05	2,227 (646)

Abbreviations: AUD: Australian dollars, GHC: Ghana cedis, DALYs: Disability adjusted life years, ICER: incremental cost effectiveness ratio. Exchange rate: 1 GHC is equivalent to 0.29 AUD.

Scenario analysis: Noncompliance to tamoxifen treatment regimen

Table 7-29 presents the ICER when the benefit of tamoxifen is reduced due to noncompliance with treatment regimen. As anticipated, the QALYs gained reduced (compared to the base case where the noncompliance rate was zero) due to noncompliance and was indirectly proportional to the percentage reduction in the benefit of tamoxifen: the higher the reduction, the lower the QALYs gained. Consequently, the higher the reduction in the benefit of tamoxifen, the higher the ICER.

Table 7-29: ICER for noncompliance to tamoxifen regimen

Percentage reduction in benefit of tamoxifen	Incremental cost (GHC(AUD))	QALYs gained	ICER (GHC (AUD)) /QALY gained
32% reduction	2,324 (674)	0.88	2,641 (766)
16% reduction	2,350 (682)	1.13	2,080 (603)
5% reduction	2,347 (681)	1.30	1,805 (523)

Abbreviations: AUD: Australian dollars, GHC: Ghana cedis, ICER: incremental cost effectiveness ratio, QALYs: quality adjusted life years. Exchange rate: 1 GHC is equivalent to 0.29 AUD.

Probabilistic sensitivity analysis (PSA)

Figure 7-7 and Figure 7-8 present the PSA results (CEAC and scatter plot of ICER) for the early breast cancer model. Ghana has not estimated or adopted a WTP threshold for making funding decisions. Therefore, authors reporting economic evaluation studies have relied on the WHO threshold (currently withdrawn) to ascertain the cost effectiveness of a health technology. This study used the best available WTP threshold value for Ghana, estimated by Woods et al. (282)[37] to determine the cost effectiveness of tamoxifen, given the data available: WTP of GHC 4,337 (AUD 1,258). Hence, at a WTP of GHC 4,337 (AUD 1,258), the

[37] Woods et al. predicted the cost effectiveness thresholds (CET) of a number of countries whose GDP per capita for the year 2013 was available from the World Bank database. They estimated the CET based on opportunity cost (they applied those estimated in a previous work, from the UK National Health Service to all countries), and estimates generated from the relationship between a country's GDP per capita and the value of a statistical life (VSL), under a series of assumptions. VSL is derived by estimating individual's WTP to reduce mortality. One of their assumptions was that the variation of VSL across countries is a function of their GDP per capita. Also, that the elasticity of VSL can provide information about the income elasticity of CET under the assumption that the income elasticity of the VSL is equal to that of the value of a life-year, which will in turn be equal to the income elasticity of the value of a morbidity adjusted life year such as QALYs.

probability that tamoxifen is cost effective compared to no tamoxifen for the adjuvant treatment of early breast cancer in pre- and peri-menopausal women is 0.80. The probability that tamoxifen is cost effective when the threshold is recalculated using the GDP per capita for year 2017, WTP of GHC 3,843 (AUD 1,115), was 0.78.

In addition, the probability that tamoxifen was cost effective compared to no tamoxifen at the patented and current market prices of tamoxifen was 0.00 and 0.68 respectively compared to 0.80 for the NHIS reimbursement price in the base case.

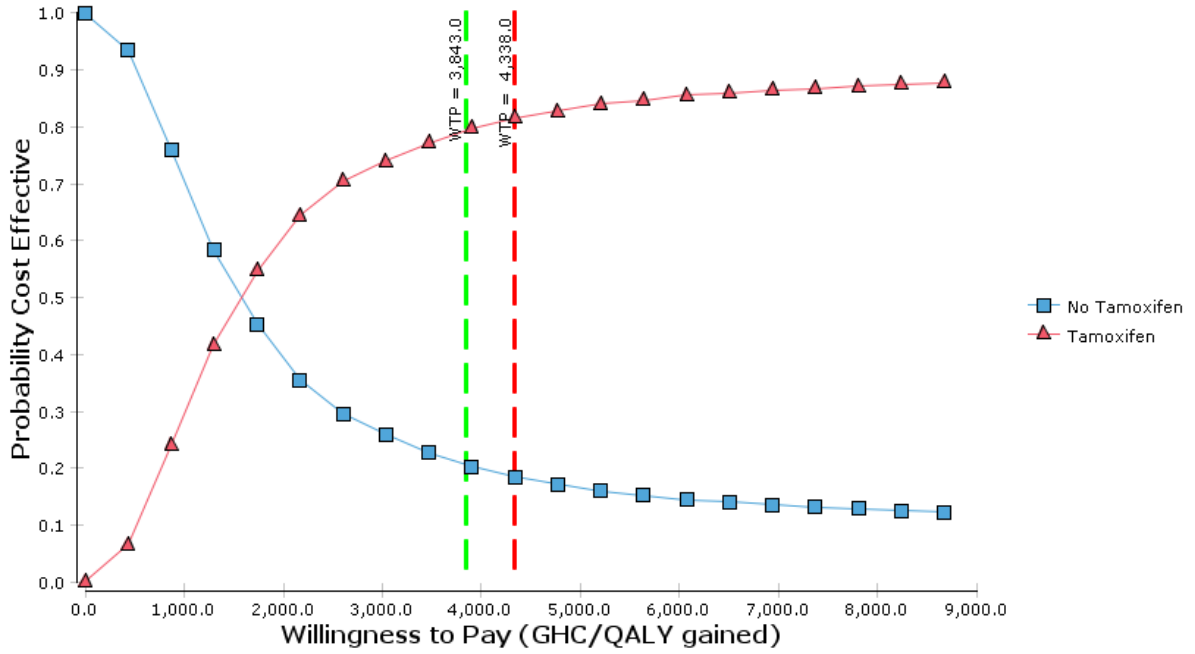
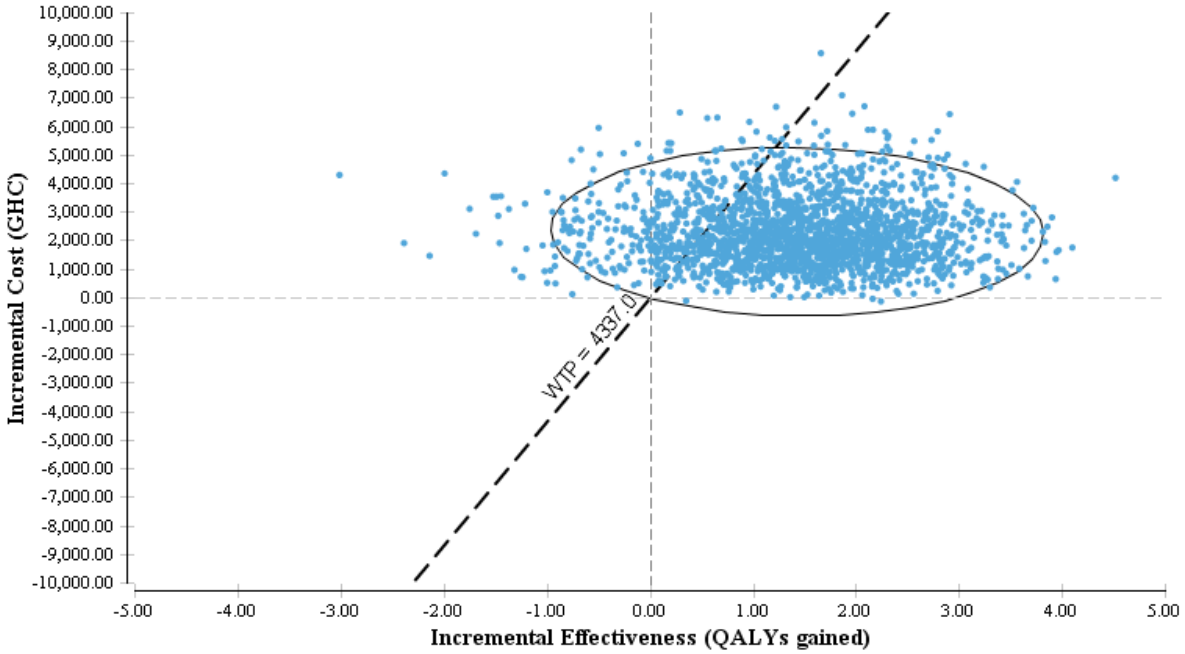


Figure 7-7: Cost effectiveness acceptability curve for the early breast cancer model



Source: Calculated in TreeAge using 2,000 simulations.
Note: Negative (-ve) QALYs rarely cost saving.

Figure 7-8: Scatter plot of ICER for the early breast cancer model

Table 7-30 compares the ICERs of the deterministic and probabilistic results. The mean ICER from the PSA was approximately the same as the deterministic ICER: GHC 1,694 (AUD 491), which is expected when the distributions used for the PSA are satisfactory.

Table 7-30: Deterministic versus probabilistic ICER - early breast cancer model

Type of result	Incremental cost (GHC (AUD))	QALYs gained	ICER (GHC (AUD))/ QALY gained
Deterministic result	2,338 (678)	1.38	1,694 (491)
PSA result, mean	2,308 (669)	1.38	1,673 (485)
PSA result, median	2,310 (700)	1.48	1,561 (453)

Abbreviations: AUD: Australian dollars, GHC: Ghana cedis., QALYs: quality adjusted life years, ICER: incremental cost effectiveness ratio. Exchange rate: 1 GHC is equivalent to 0.29 AUD.

7.4 Discussion

7.4.1 Summary of major findings

A pre- or peri-menopausal woman who takes tamoxifen for five years for the adjuvant treatment of breast cancer gains an additional 1.38 QALYs on average, compared to those who

do not. The ICER (cost per QALY gained) was estimated at GHC 1,694 (AUD 491), which is highly cost effective at a WTP of GHC 4,337 (AUD 1,258) (0.80 probability of being cost effective).

The cost of tamoxifen was the key driver of the ICER. Hence, tamoxifen was unlikely to be cost effective (0.00 probability) at the estimated patented price: ICER = GH 36,843 (AUD 10,684). This suggests that even highly effective patented medicines such as tamoxifen are unlikely to be cost effective until lower cost generic alternatives become available. It is therefore prudent for Ghanaian decision makers to focus on older health technologies. The probability that tamoxifen was cost effective at the current market price was 0.68.

In addition to the cost of tamoxifen, the ICER was most sensitive to the utility weight used for the disease-free with no recurrence state. A change in the structure of the model did not change the ICER. Noncompliance with the tamoxifen regimen increased the ICER, lowering the probability that tamoxifen would be cost effective compared to no tamoxifen.

Extending tamoxifen therapy for 10 years did not result in additional QALYs gained compared to that of five years, but it increased the ICER by 61% to GHC 2,723 (AUD 790) from GHC 1,694 (AUD 491). In a subgroup analysis, women aged less than 45 years gained more QALYs compared to those aged 45 to 54 years. Subsequently, the ICER for the younger women was less than that of the older women.

The ICER using DALYs averted was higher than the ICER using QALYs gained. This has implications on how cost effective tamoxifen is, and subsequently decisions made by policy makers. The differences and direction of the ICER depending on the benefit measure used remains unresolved in the literature, although methodological differences in its elicitation have been acknowledged as the main cause. Studies that have attempted to compare the impact of using these different measures of health outcomes on decision-making have reported two

different trends: either DALYs averted were more than QALYs gained (76, 89, 91) or vice versa (76, 91), for the same intervention. The defining differences between these studies were in the age of onset and duration of disease. Disease onset in early years resulted in more DALYs averted than QALYs gained and vice versa.

7.4.2 Comparison with other published economic evaluations

The results of this study are not directly comparable to the results of other evaluations reviewed in Chapter 6, section 6.3, with the exception of one study: Yang et al. (224). This is because among other things such as the differences in study setting and clinical practice, these studies compared tamoxifen to anastrozole and their study population was postmenopausal. However, since all the studies sought to assess the cost effectiveness of HTBC, an attempt is made to compare some of the model characteristics and the key model parameters that drive the ICER.

Yang et al. (224) evaluated the cost effectiveness of adjuvant tamoxifen therapy compared to no tamoxifen for Korean breast cancer patients from a societal perspective. In this study, efficacy data was estimated from a meta-analysis of 20 RCTs, whereas Yang et al. (224) used as their source of efficacy data an observational study limited by an inability to control for unobserved events and other confounding factors. In addition, while this study used a Markov model to synthesise the data, Yang et al. were not clear about the type of decision analytic model used. Their efficacy endpoint and health outcome were overall survival and life years saved respectively. In contrast, this study used time to recurrence, and both QALYs gained and life years saved. A limitation of using life years gained as the measure of benefit is the inability to account for the quality of life of patients.

It is evident from this study that the quality of life of patients contributes to the overall ICER estimated. Patients in this study gained more QALYs compared to life years. Thus, incorporating QALYs made the intervention more cost effective compared to when only life

years were used. The analysis by Yang et al. included both women with early and advanced breast cancer, therefore, for the purposes of this discussion, only the results of hormone receptor positive women with early breast cancer will be considered.

Yang et al. estimated an ICER of 1,939 USD (GHC 8,860) for all hormone receptor positive women, 1,137 USD (GHC 5,195) for women less than 40 years and an average of 1,516 USD (GHC 6,929) for women less than 50 years. Their ICERs are more than twice those estimated for this study. As well as the differences discussed above, the differences in ICERs could be attributed to the differences in the relative costs and prices of resources, different clinical practice and subsequent resource use, different year of estimation (that could affect the costs of resources especially of tamoxifen) and the perspective of the analysis. The costs due to productivity loss (that is lower productivity) and terminal care that were included in Yang et al.'s study could have also contributed to the higher ICER observed.

Some of the findings of the remaining economic evaluations reviewed are consistent with this study. The ICER was sensitive to the time horizon of the model with a longer time horizon resulting in a lower ICER. In addition, ICERs were not sensitive to the costs with the exception of the cost of tamoxifen. Discount rates also had little effect on the ICER. Conversely, while the ICER of this study was most sensitive to the utility weight for disease-free state, those (225, 237) that reported the impact of change in utility weight found otherwise. For the studies that reported the unit cost of tamoxifen tablet per day, 27% reported a higher unit cost while 73% reported a lower unit cost than the current market price of tamoxifen in Ghana.

7.4.3 Strengths of the evaluation

The model developed in this thesis to evaluate tamoxifen therapy for pre- and peri-menopausal women with early breast cancer was based on rich data in terms of clinical effectiveness. For example, the efficacy estimates were based on a meta-analysis of 20 clinical trials that observed

effectiveness for more than 15 years, which was the same time horizon used in the model. Hence, the extrapolation of survival results and its limitations were avoided. In addition, the effectiveness data was presented over different periods that better reflect the effects of tamoxifen after therapy is completed. Again, even though the clinical trials used for meta-analysis had no study site in Ghana and or other developing countries, in the absence of country specific data, aggregated data from different trials as carried out by the EBCTCG for early breast cancer is considered the best source of efficacy data. Perhaps a group of researchers could be convened to aggregate existing efficacy data on different technologies for use by developing countries that lack such data.

Unlike the reviewed evaluations, this study used utility estimates derived from a meta-regression analysis with consideration of country specific treatment algorithms and the epidemiology of breast cancer. Furthermore, resource use was estimated in accordance with the current Ghanaian clinical treatment algorithm of breast cancer. The unit costs of all resource use were derived from Ghanaian sources and were specific to the perspective of analysis i.e. the payer; therefore these represented a true reflection of costs to the government.

This evaluation assessed the cost effectiveness of tamoxifen for the adjuvant treatment of pre- and peri-menopausal women with early breast cancer, a subject that has not been thoroughly addressed in the literature. It also explored the effect of taking tamoxifen for 10 years in addition to five years.

7.4.4 Key limitations of the evaluation

A key limitation of this analysis is its reliance on clinical expertise to define resource use and to estimate the associated costs. The best source of information about resource use would have been a database linked to diagnosis and treatment, but there is no such thing in Ghana. In addition, there was no published study on the costs of treatment in the different stages of breast

cancer, nor are there any written guidelines for the treatment of breast cancer. Therefore, expert opinion was considered the best available source of information, though this might have resulted in over- or under- estimation of costs.

Nonetheless, this bias was reduced as much as possible by conducting a second interview with the same expert in order to reconcile any differences in information provided in the previous interview. In addition, advice from a second clinical expert and published international guidelines were used to validate the opinion of the Ghanaian clinical expert. There were differences between resource use in Ghana and that reported by international guidelines and subsequently clinical trials protocols. For example, while it is expected that women taking tamoxifen had abdominal ultrasound to detect endometrial cancer due to adverse effects of tamoxifen, this is not done in Ghana. The main reason for the difference was attributed to unavailability of resources and inability of patients to afford it.

The frequency with which patients experienced vaginal bleeding, pulmonary embolism and deep vein thrombosis may have been underestimated. It may be that some patients can experience these adverse events more than once during the period of tamoxifen therapy. The proportions of patients who experience adverse events may have also been over or underestimated. It is also possible that some patients will experience other adverse events not included in this model, such as endometrial cancer, in the future. Increases in the number of adverse events experienced and the proportion of women assumed to experience them would have led to an increase in the ICER. Exclusion of costs and disutilities due to adverse events in this study resulted in a 20% decrement of the base ICER while a 50% increase in the utility lost due to adverse events resulted in a 2% increase in the ICER. This suggests that adverse events were not a major driver of the ICER for this evaluation.

Another limitation concerning the clinical efficacy data adopted for use in the model is the fact that this study combined women aged less than 45 and those aged 45 to 54 years to represent pre- and peri-menopausal women. This may not be a true reflection of the menopausal status of women as it is likely that some women could reach menopause earlier than 54 years. To address this limitation, a subgroup analysis was conducted for these two age groups. Heterogeneity due to age was not modelled in the base case due to the lack of patient level data to conduct it. Modelling was done assuming that patients were a cohort of women aged 49 years.

Due to the unavailability of quality data on country specific data breast cancer mortality rates, this model used estimates reported by the meta-analysis, which may vary from what actually occurs in Ghana.

The rate of noncompliance seen in real world clinical practice was not factored into the base model. In a sensitivity analysis noncompliance was observed to have an impact on the effectiveness and cost effectiveness of tamoxifen. Noncompliance with tamoxifen treatment led to a reduction in the effectiveness of the drug and consequently, decreased numbers of QALYs gained and a higher ICER. Nonetheless, the impact of noncompliance on the ICER and probability that tamoxifen will be cost effective is dependent on reliant on the number of women who will not comply and the extent of their noncompliance which subsequently informs the percentage reductions in the benefit of tamoxifen.

Lastly, the assumptions used in the model may contribute to the uncertainties in the estimated results, as seen with all models. However, these were addressed by conducting sensitivity analyses to assess the effects of these assumptions and all parameters used on the ICER.

7.4.5 Key issues with translation of data to the Ghanaian context for economic evaluation and its implications on HTA conduct in Ghana

One key issue with translating data from other countries to Ghana for economic evaluation is the limited country specific data required for the translation. For example, the recommended good practice of transferring clinical effectiveness data across jurisdictions require that evaluators apply the relative risk reduction of health states observed in the trial to the baseline risk of the setting under evaluation to make it country specific. This could not be done for the current evaluation because of the lack of country specific data on the baseline risk of the health states used in the model. The lack of utility values for a healthy Ghanaian prevented an assessment of the strength of assumptions used in estimating utility values for breast cancer health states used in this model. Therefore, in pursuing HTA, Ghana may have to put measures in place for collecting this kind of data.

Another potential limitation in conducting economic evaluation in Ghana is the fact that, in the absence of country specific economic data (such as clinical efficacy and utility values), the data available from other jurisdictions for transformation may be very limited, especially for clinical efficacy data. This is due to the large differences in clinical practices between Ghana and most developed countries where clinical trials tend to be conducted, and differences between treatment protocols of the clinical trials and Ghana. Hence, an evaluator may have to rely on data that apply to Ghana, which may not be the best source in terms of bias and the strength of the evidence.

This study has demonstrated that the differences in clinical practice, especially those that are cultural and context-specific, can affect the choice of comparator. This is because what may be widely accepted and used as an alternative treatment to the technology under evaluation may not be accepted in the Ghanaian setting. Other comparators that may be accepted culturally may also not be an option because of the acquisition cost, such as in the case of patented

technologies. Subsequently, the choice of an appropriate comparator is restricted, as are the clinical efficacy data needed to conduct the evaluation. Because of these factors, 'no treatment' may be the best comparator for an evaluation. Hence, these should be taken into account (in terms of choosing a comparator) when developing a guideline for the conduct of economic evaluation in Ghana. Also, even though many clinical trials conducted in recent years have been condemned for using basic supportive care or placebo as the comparator for a new technology, this practice is ideal for Ghana. In addition, Ghana and other developing countries will need to conduct an indirect treatment comparison to get the right comparator.

Again, the differences in clinical practice limits the transferability of economic evaluation studies from a different country to Ghana for HTA. Consequently, the probability of Ghana relying of economic evaluations conducted in other settings for a country specific HTA appraisal due to the limited human capacity is further restricted. This also applies to adopting HTA findings from other countries to Ghana for similar reasons.

It is likely that in Ghana, at least for the foreseeable future, economic evaluators will have to rely on clinical experts for relevant inputs into the model. As much as this comes with its own limitations, in the absence of necessary data, expert(s) opinion(s) are the best source. Instances where the inputs of clinical experts would be required include estimating resource use for treatment and establishing baseline risk, incidence and prevalence of a condition. Therefore, it is judicious for policy makers to educate clinicians and specialists on the importance of HTA and their likely role in conducting appraisals in the short to medium term, while measures are put in place to collate this information for easy access by researchers in the long-term.

Even though this evaluation relied on the NHIS reimbursement price list, the findings revealed that there can be instances where the market price of medicines may vary from the NHIS reimbursement price. This is due to fluctuations in the exchange rate affecting the prices of

imported goods (including medicines and other health technologies). Patients who want to receive these treatments are therefore required to make informal co-payments to make up the difference. These potential differences in costs would need to be recognised and acknowledged in future economic evaluations conducted in Ghana even if these are conducted from the payers' perspective. Subsequently, to reflect the true costs and cost effectiveness of a health technology, a database with the current prices of health technologies would have to be developed and updated regularly.

The implications of these challenges to the conduct of HTA in Ghana is that while it is possible to conduct a full economic evaluation in the Ghanaian context for HTA, evaluators would need the inputs of clinical experts and may have to rely on limited data sources for economic evidence on efficacy and utilities. Additional Ghanaian data would also be needed in the future for HTA, as the current Ghanaian data available are not sufficient to conduct a full economic evaluation.

7.5 Conclusion

This chapter presented a cost utility analysis of tamoxifen for the adjuvant treatment of early breast cancer among pre- and peri-menopausal Ghanaian women. Differences in practices in Ghana compared with other jurisdictions (such as differences in clinical management algorithms) restricts the extent to which international data could be used in evaluations. Notwithstanding this, the study has demonstrated that data from the literature on utility weights and efficacy of tamoxifen from different jurisdictions can be transformed and used together with data on resource use and costs in Ghana to conduct an economic evaluation. However, this approach comes with several limitations that were addressed in a sensitivity analysis.

This evaluation has also demonstrated that, in the absence of all the required data needed to populate a 'standard model', its structure can be adjusted to suit the data available without

having a significant impact on the results. A major challenge for this study was the unavailability of data on resource use and the lack of a written standard guideline for the treatment of breast cancer in Ghana, hence reliance on expert opinion. Thus, Ghana will need to invest in data collection and management to provide suitable data for use in economic evaluations and HTA.

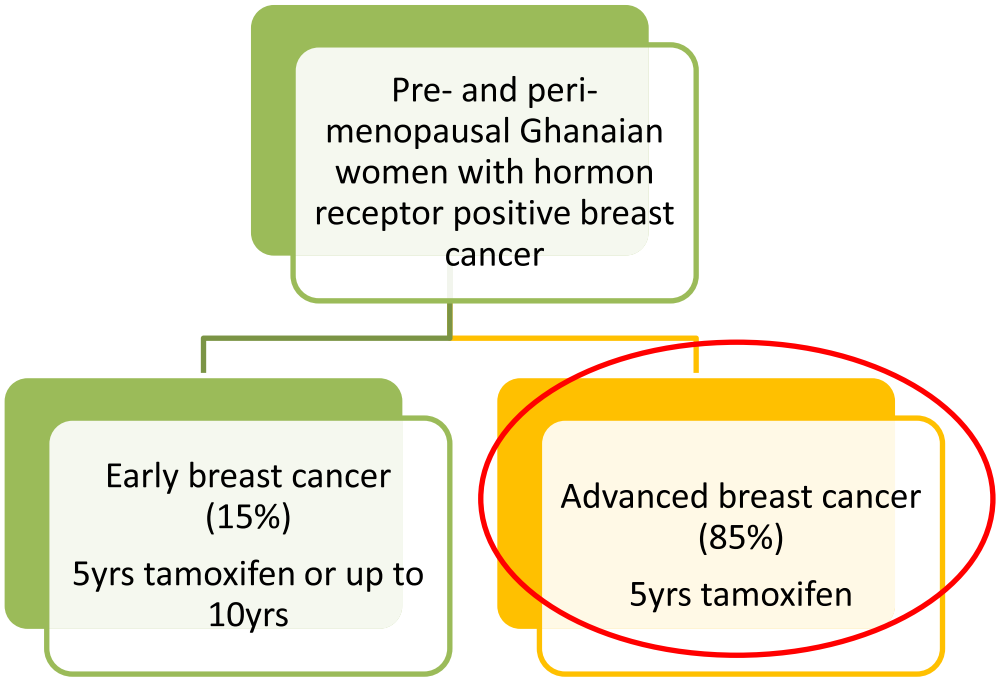
The hormonal treatment of early breast cancer among pre- and peri-menopausal Ghanaian women with tamoxifen compared to no tamoxifen was cost effective at the WTP used for this study. The cost of tamoxifen is a major driver of the ICER. As mentioned in Chapter 6, only 15% of Ghanaian women with breast cancer are diagnosed at the early stages, indicating the need to assess the cost effectiveness of tamoxifen to the population with the highest burden (advanced breast cancer). This evaluation is conducted in the next chapter.

8 HTA IN GHANA: ECONOMIC EVALUATION OF TAMOXIFEN FOR THE HORMONAL TREATMENT OF ADVANCED BREAST CANCER IN PRE- AND PERI-MENOPAUSAL WOMEN

8.1 Introduction

Chapter 7 demonstrated that tamoxifen for the hormonal treatment of early breast cancer was cost effective. This chapter addresses the question of whether tamoxifen is cost effective for the hormonal treatment of advanced breast cancer compared to no tamoxifen. This is because most Ghanaian women diagnosed with breast cancer present at the advanced stage (Figure 8-1).

Chapter 6 established that no direct evidence comparing tamoxifen with best supportive care was available on the efficacy of tamoxifen for the model. Therefore, this chapter describes how the indirect evidence on the efficacy of tamoxifen was identified and transformed for use in the current model. This is presented in section 7.2 together with transformation of utility values, structure and assumptions used, and methods utilised to examine the robustness of model inputs for the base case results. Section 7.3 presents the findings of the base case and sensitivity analysis. The findings of the evaluation are discussed considering existing literature, its strengths, limitations and implications on HTA conduct in Ghana in section 7.4. Section 7.5 concludes the chapter by eliciting the key findings and their implications on policy and future research.



Note: The arm highlighted in a different colour and with an oval is the population of focus for the evaluation.

Figure 8-1: Proportions of Ghanaian pre- and peri-menopausal women with breast cancer according to stage of disease

8.2 Methods

The economic evaluation was conducted and reported according to the CHEERS checklist (see Appendix 6 Table 11-10 for the CHEERS statement). The major features of the model are presented in Table 8-1, and further explained in the sections below.

Table 8-1: Summary of model characteristics

Model characteristics	Inputs used in the base case model
Type of evaluation	Cost utility analysis
Perspective of analysis	Health system (payer)
Time horizon	10 years
Cycle length	Monthly
Duration of treatment	5 years
Mean age of entry into model	49 years
Choice of health outcome	QALYs
Estimation of costs	Bottom-up approach
Date of resource estimation and unit costs	2017
Discount rate	3%

8.2.1 Structure of the model

A Markov model was chosen as the most appropriate model. A one-month cycle was adopted due to the rate at which patients with advanced breast cancer are likely to progress from one state to another, and in accordance to other models reviewed. A 10-year time horizon was chosen with input from a Ghanaian clinical expert, although most patients with advanced breast cancer are not likely to survive beyond 10 years. In accordance with the mean age of breast cancer presentation in Ghana, all patients entered the model at age 49. Heterogeneity due to age was not modelled for in this study due to a lack of patient level data. Thus, modelling was conducted assuming that patients were a cohort of 49 year-old Ghanaian women. The effectiveness of tamoxifen was measured as the number of QALYs gained for the base case analysis and as the number of DALYs averted in a sensitivity analysis.

The base case analysis was estimated from a health system perspective. However, a societal perspective was evaluated in a sensitivity analysis for completeness. This is because in Ghana, patients diagnosed with advanced breast cancer are largely cared for by their family members, and there are no palliative care services in the country. Patients only go to hospital for treatment of complications and other symptoms such as breathlessness due to metastases of breast cancer. In the absence of any symptoms or ailments requiring medical attention, family members visit the oncology OPD every six months to obtain the necessary medication such as endocrine therapy and analgesics. The ICER was calculated using Equation 2 from Chapter 7.

Of the three studies that evaluated the cost effectiveness of tamoxifen for advanced breast cancer (Chapter 6 section 6.3), one did not present a structure (229), and the one that evaluated both advanced and early breast cancer did not have a clear model structure for advanced and early breast cancer separately (224). The remaining study in which a model structure was presented only included two states: response to therapy and no response to therapy (241).

The present study used three health states: pre-progression (progression-free), progression and death (due to all causes including breast cancer) (Figure 8-2 and Figure 8-3), in line with the natural history of advanced breast cancer. Patients in a pre-progression state are those diagnosed with advanced breast cancer who have received initial treatment and either responded or remain in a stable condition. Patients in the progression state are defined as those whose disease progresses irrespective of any form of treatment they might have received. The death state includes patients who die from breast cancer or other causes. Patients in each state receive tamoxifen as a hormonal therapy or not, depending on the treatment arm she is allocated to. The transitions possible in the model are presented in Table 8-2.

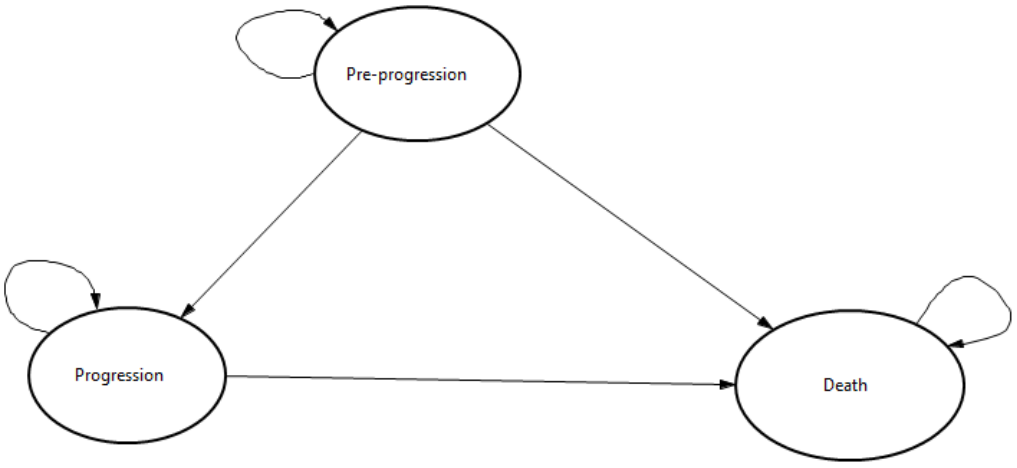
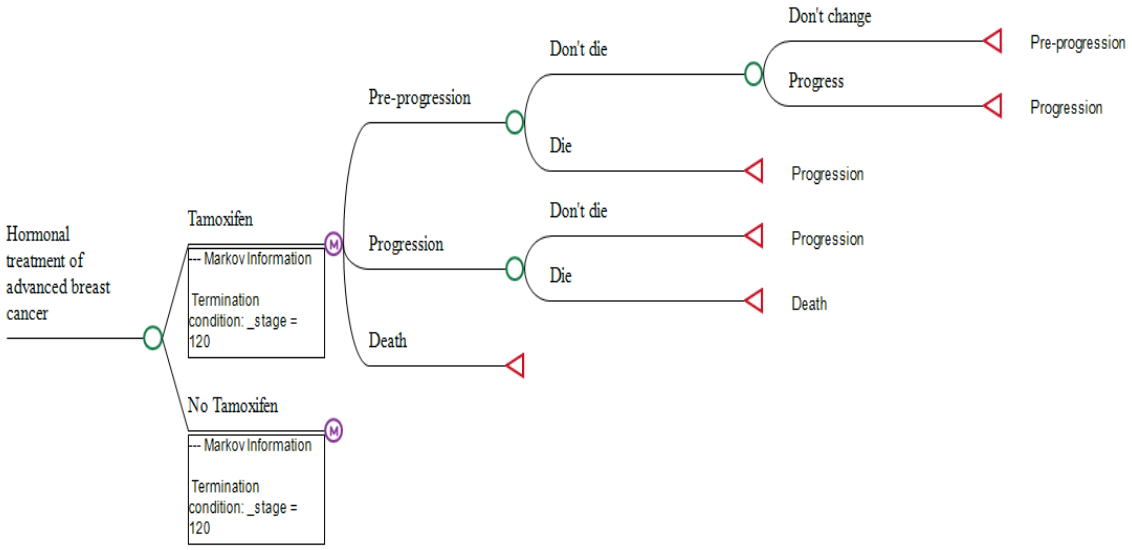


Figure 8-2: Markov transition states



Note: The model was created in TreeAge software; hence, this diagram presents the model structure as used in the software.

Figure 8-3: Economic model for the adjuvant treatment of advanced breast cancer in pre- and peri-menopausal women

Table 8-2: Possible transitions in the advanced breast cancer model

Health state	Transitions	Source of data used to derive transition probability
Pre-progression		
	Remain in pre-progression state	Klijn et al. 2000 Yang et al. 2010
	Progression	Klijn et al. 2000 Yang et al. 2010
	Death	Ghana life table Klijn et al. 2000 Yang et al. 2010
Progression		
	Remain in progression state	Klijn et al. 2000 Yang et al. 2010
	Death	Ghana life table Klijn et al. 2000
Death	Absorbing state	Ghana life table Klijn et al. 2000

8.2.2 Additional assumptions used in the advanced breast cancer model

In addition to the assumptions made in the early breast cancer model (assumptions one to five[38]), it was assumed that patients who moved from a pre-progression state to a progression state did not discontinue tamoxifen. This is in accordance with current treatment practices in the Ghanaian health system.

8.2.3 Model inputs

Efficacy of tamoxifen

From the systematic search conducted in Chapter 6 section 6.5.1 no RCT was identified with direct evidence for the comparators under study. This is a common problem in HTA, therefore the next best method of estimating the clinical efficacy data is via an indirect comparison using a common comparator. Table 8-3 presents the various comparators used in the studies identified from the search. Four of these were meta-analysis of RCTs that compared ovarian function suppression with or without tamoxifen or chemotherapy for the hormonal treatment of either early or advanced breast cancer as defined in Table 8-3 and Chapter 6, section 6.5.1, Table 6-4. Of the remaining three single studies, only one (283) had tamoxifen as a comparator (secondary). From the search, no common comparator was found to enable an indirect comparison.

[38] For assumption three, in this model, patients incurred costs and disutilities associated with adverse events when they entered the pre-progression state.

Table 8-3: Summary of studies reporting the efficacy of tamoxifen for the adjuvant treatment of advanced breast cancer

Study	Primary comparator	Secondary comparator
Falkson et al. 1995	Ovarian ablation plus chemotherapy	Chemotherapy
*Crump et al. 1997	Ovarian ablation	Tamoxifen
*Sawka et al. 1997	Tamoxifen	Ovarian ablation
Klijn et al. 2000	Ovarian suppression plus tamoxifen	Tamoxifen, ovarian suppression
Klijn et al. 2001	Ovarian suppression plus tamoxifen	Ovarian suppression
***Zhang et al. 2017	Ovarian ablation or suppression	Tamoxifen
	Ovarian ablation or suppression plus tamoxifen	Tamoxifen
	Ovarian ablation or suppression plus tamoxifen	Chemotherapy
	Ovarian ablation or suppression plus chemotherapy	Chemotherapy
	Ovarian ablation or suppression	Chemotherapy

*Meta-analysis of RCTs of adjuvant treatments for breast cancer in pre-menopausal women
**Meta-analysis of RCTs comparing tamoxifen with ovarian function suppression treatments in pre-menopausal women
***Meta-analysis of adjuvant treatment of both early and advanced breast cancer in pre-menopausal women

Therefore, an additional manual search was conducted to identify cohort or case studies comparing tamoxifen with no tamoxifen or any other comparators. One cohort study was identified that compared tamoxifen to no tamoxifen (224) (identified through the systematic review conducted initially on the economic evaluation studies on tamoxifen for HTBC). Thus, this study together with the RCT (283) which compared the effectiveness of tamoxifen with an ovarian function suppressant were selected as the best sources of data to estimate the clinical efficacy of tamoxifen for the hormonal treatment of advanced breast cancer.

The cohort study retrospectively evaluated the overall survival of Korean women diagnosed with breast cancer who received tamoxifen or no tamoxifen as adjuvant treatment. Apart from the differences in the study designs, there were also marked differences in the baseline characteristics of the population included in these studies. For instance, while the breast cancers of 94% of the pre-menopausal women in the RCT had metastasised (stage IV), all women in the cohort study were in the locally advanced stage (stage III). The characteristics of these studies are compared in Table 8-4.

Table 8-4: Comparison between the two main sources of efficacy data: RCT and Cohort study

	Klijn et al. 2000	Yang et al. 2010
Type of study	RCT	Retrospective cohort study
Comparators	Tamoxifen Luteinizing hormone-releasing hormone agonist (LHRH-A) Tamoxifen + LHRH-A	Tamoxifen No tamoxifen
Study population	Pre-menopausal women with Stage III and IV breast cancer	Pre-menopausal women with Stage III breast cancer
Clinical effectiveness endpoints	Median progression-free state Median overall survival Actuarial survival rate Median survival after progression	Mean survival rate
Other data	Proportions of patients with: Complete remission Partial remission Stable disease Progressive disease	None reported
Duration of study (follow-up)	7.3 years	9 years
Number of patients	161	20,765
Hormone receptor positive patients	Yes	Yes
Median/mean age for tamoxifen use by patients	42 years	47.5 years

Table 8-5 presents a comparison between the population and intervention characteristics of the studies used as sources of efficacy data and the Ghanaian population expected to use tamoxifen, to assess the applicability of these studies to the Ghanaian context. Both studies were conducted in high-income countries and have similar characteristics to each other such as hormone receptor status, prior test, prior treatment and duration of treatment. These characteristics are similar to those observed in the Ghanaian population.

Table 8-5: Comparison between target population and population efficacy data from from studies being used

Characteristics	Ghanaian population	Population from Klijn et al. 2000	Population from Yang et al. 2010
Age	Mean age at diagnosis and subsequent tamoxifen use is 49 years	Median age for tamoxifen use by patients was 42 years	Mean age for tamoxifen use by patient was 47.5 years
Stage of breast cancer	Stage III and IV	Stage III and IV	Stage III

Characteristics	Ghanaian population	Population from Klijn et al. 2000	Population from Yang et al. 2010
Hormone receptor status	Hormone receptor positive	Hormone receptor positive Receptor status unknown	Hormone receptor positive
Prior test	Hormone receptor status Histology to confirm cancer	Hormone receptor status Histology to confirm cancer	Hormone receptor status Histology to confirm cancer
Prior treatment	Lumpectomy (breast conservation surgery)/mastectomy Adjuvant chemotherapy	Mastectomy/breast conserving surgery With or without adjuvant chemotherapy treatment	Mastectomy/breast conserving surgery Adjuvant Chemotherapy
Duration of tamoxifen intake	5 years	5 years	5 years
Dose of tamoxifen	20mg daily	20mg twice daily	20mg daily
Country	Ghana	The Netherlands, France, Belgium, South Africa, Poland, Spain, Austria, Germany, Hungary	Korea

Abbreviation: mg: milligrams.

Klijn et al. (283) was chosen as the main source of efficacy data because as an RCT its evidence is stronger than that from a retrospective cohort study. Unlike the cohort study, randomisation of participants in a RCT study ensures that the effects of the comparators (including the tamoxifen arm being used in the present study) are void of confounders, thus strengthening the internal validity of the results of Klijn et al. (283), and confidence in the results. However, this is not relevant in terms of its applicability to the Ghanaian context. The external validity of a study enhances its applicability to other contexts. Despite the strength of a cohort study is in the external validity of the results, the study by Yang et al. doesn't apply to the Ghanaian context compared to the RCT by Klijn et al. This is because of the differences in the composition of the stage of presentation of advanced breast cancer between Ghanaian and Korean women: Stage III and IV versus Stage III only, compared to the trial population that had similar characteristics to the Ghanaian population (Table 8-5). Consequently, the efficacy estimates from Klijn et al.'s RCT was chosen over the cohort study by Yang et al. (224) as the primary source as it is more relevant to Ghana.

The comparators (see Table 8-3) used in the trial were appropriate at the time the trial was conducted. The recommended dose of tamoxifen was 40mg at the time of the study, however, further research demonstrate no difference between 20mg and 40mg daily dose of tamoxifen which resulted in the adoption of 20mg daily dose of tamoxifen in the adjuvant setting to reduce the incidence of adverse events and toxicity due to the drug (212, 258).

Therefore, the efficacy of the tamoxifen arm of this model was derived from the tamoxifen arm of the RCT. To estimate the efficacy of the no tamoxifen arm, the hazard rate for the tamoxifen arm of the RCT (denoted by x) was weighted by the hazard rate of the no tamoxifen arm in the cohort study (denoted by z). In order for this estimation to hold, it was assumed that both arms include the same number of patients. A second assumption was that the overall survival rate of patients in the no tamoxifen arm was the same as the rate at which they progressed from stable/responsive disease to progressive disease. To derive z, the median survival rates for both arms of the cohort study were calculated (see Equation 5 for formulae).

$$Median\ survival\ time\ (MST) = \frac{In\ (2)}{Hazard\ rate\ (HR)} \qquad \text{Equation 5}$$

Then z was estimated by dividing the HR for the no tamoxifen arm by that of the tamoxifen arm (HR of no tamoxifen/HR for tamoxifen). After estimating the hazard rate of the tamoxifen arm of the RCT, x, the hazard rate of the 'simulated' no tamoxifen arm of this model, y, was calculated by multiplying x by y. The median overall survival time, time to progression and survival after progression were taken from the tamoxifen arm in the RCT. Those for the no tamoxifen arm were estimated from the HR calculated (y) (See Equation 6).

$$Hazard\ rate\ (HR) = \frac{In(2)}{Median\ survival\ time\ (MST)} \qquad \text{Equation 6}$$

The median survival times (MSTs) were converted to instantaneous hazard rate (IHR) of time to progression, overall survival and survival after progression for both the tamoxifen and no tamoxifen arms of this model (see Equation 7 for formulae).

$$Instantaneous\ hazard\ rate\ (IHR) = -\frac{In\ (0.5)}{Median\ survival\ time\ (MST)} \qquad \text{Equation 7}$$

The IHRs were then converted to monthly transition probabilities assuming a constant rate of progression, overall survival and survival after progression (261) (i.e. an exponential function) (see Equation 8 for formulae).

$$Monthly\ transition\ probability\ (MTP) = 1 - EXP\ (-IHR) \qquad \text{Equation 8}$$

Table 8-6 presents the monthly transition probabilities used in the model. The calculation of efficacy estimates used in this model is detailed in Appendix 6, Table 11-12. The methodological approach used is limited by the fact that there are differences between the populations of the two studies used and between the studies and the Ghanaian population. To account for the differences between some of the characteristics of the Ghanaian population and participants in the clinical trial, a sensitivity analysis was conducted on variables such as age at diagnosis, probability of death after progression and probability of death without progression. Moreover, in the real world, the probability of transitioning from one health state to the other may not be constant over the time horizon of the model as assumed in the estimation.

Table 8-6: Monthly transition probabilities for advanced breast cancer model

	Tamoxifen			**No tamoxifen**		
	Estimate	CI	SE	Estimate	CI	SE
Progression from progression-free survival	0.010	0.007 – 0.013	0.055	0.013	0.009 – 0.017	0.070
Breast cancer death from progression	0.025	0.013 – 0.032	0.087	0.032	0.017 – 0.041	0.109
Breast cancer death from progression-free survival	0.021	0.016 – 0.026	0.140	0.027	0.020 – 0.034	0.176

Abbreviations: CI: confidence interval, SE: standard error.
Source: Derived from Klijn et al. 2000 and Yang et al. 2010

Utilities and disutilities

To estimate the utility weights for the progression-free and progressed health states in the advanced breast cancer model, the coefficients estimated by Peasgood et al. (248) [39] were used. This was done by assuming treatment type (chemotherapy), response to treatment (stable), no side-effects, standard gamble method of evaluation and the community's values as the baseline values. Other inputs such as the characteristics of, and treatments received by, patients in these states were obtained from a Ghanaian clinical expert. Patients in the progression-free state included both those who were stable and those who responded to treatment. Therefore, the utilities for patients in progression-free and progressed states who received tamoxifen were estimated as 0.789 and 0.569 respectively.

Table 8-7 presents the derivation of utility weights for the health states using same approach as in the early breast cancer model in Chapter 7 section 7.2.3. These estimates were converted to monthly values in accordance with the cycle length of model. In addition, patients in the tamoxifen arm received additional utilities due to hormonal therapy, 0.134, and subsequently disutilities due to any related adverse events. For instance, a patient in the progression-free state receiving tamoxifen, with vaginal bleeding (utility weight of 0.07) would be allocated a utility weight of 0.719 that is utility of progression-free (0.655) plus utility due to hormonal therapy (0.134) minus disutility due to vaginal bleeding (0.07).

Table 8-7 : Utility weights estimated for the health states used in the advanced breast cancer model

Health state	Baseline variables included	Utility weights
Progression-free state		
	Constant	0.640
	Stable (0.85[a])	0.000 (0.000[b])
	Response (0.15[a])	0.097 (0.015[b])
	Community value	0.000
	Standard gamble	0.000
	No side-effects	0.000

[39] Model 2 is preferred by the authors because it has a substantially larger sample size. It was weighted by the sample size using all available utility values.

Health state	Baseline variables included	Utility weights
	All variables	0.655
Progression state		
	Constant	0.640
	Progression	-0.205
	Community value	0.000
	Standard gamble	0.000
	No side-effects	0.000
	All variables	0.435

a. Proportions of patients assumed to either remain stable or respond to treatment (source: Ghanaian clinical expert)
b. Utility value weighted by the proportion of patients experiencing that event (source: Peasgood et al. 2010).

Resource use and costs

The cost per patient per each health state constitutes costs incurred by the health system (base case), and the societal (both health system, patient and the family). Costs to the health system include costs of physician visits (which included consultation fees, laboratory tests and medicines), hospitalisation, and endocrine therapy. Costs incurred by the patient and her family includes productivity loss due to informal care, seeking treatment and illness.

In estimating costs due to productivity loss, it was assumed that the distribution of formal and informal sector workers for caregivers were the same as that reported for patients who were all women[40]. Another assumption is that the primary caregiver of the patient is a female (who can be a sibling, daughter, mother in-law, daughter in-law or mother of the patient) which is a common practice in Africa. Costs were estimated per month (equivalent to the cycle length of the model) in Ghanaian cedis (GHC) and 2017 price. The total cost of each cost item under a health state was estimated as a product of the unit cost, the proportion of patients likely to incur those costs and the frequency of use. Therefore, total costs per health state was calculated as a sum of all cost items under each health state.

[40] Resource use and all assumptions made in its estimation were based on inputs from a Ghanaian clinical expert. Costs of productivity loss due to formal and informal sector workers were taken from a study by Gyau and Nonvignon (255).

Table 8-8 describes the estimation of costs due to progression-free state. Total progression-free state costs are a sum of costs incurred by the health system, patient and family for the society. Health system cost include hospitalisation and follow-up visits. It was assumed that 10% of patients in this state would be hospitalised once in a month for treatment. Forty percent of family members were assumed to lose productive days once in a month due to caregiving. This was estimated as a sum of cost of productivity loss due to formal sector workers and non-formal sector workers. The same method was used to estimate productivity loss to patients. The total cost of progression-free state per month was estimated at GHC 653 (AUD 189): 61% (GHC 400 (AUD 116)) due to patient and family and 39% (GHC 253 (AUD 73)) for the health system.

Table 8-8: Estimation of costs due to progression-free state

Cost item	Percentage treated	Frequency of use	Unit cost (GHC (AUD))	Total cost (GHC (AUD))
Health system cost				
Physician visits				
Follow-ups with oncologist	100	0.17	26.04 (7.55)	4.43 (1.28)
General laboratory test for follow-up	100	0.17	41.15 (11.93)	7.00 (2.03)
FBC	100	1	11.74 (3.40)	11.74 (3.40)
LFTs	100	1	16.81 (4.87)	16.81 (4.87)
Kidney function test	100	1	12.60 (3.65)	12.60 (3.65)
OPD visits to treat symptoms	40	1	26.04 (7.55)	10.42 (3.02)
Cost of drugs to treat symptoms	40	1	517.77 (150.15)	207.11(60.06)
Analgesics	100	30	1.18 (0.34)	35.49 (10.29)
Haematinics	40	30	0.19 (0.06)	2.28 (0.66)
Others	40	30	40.00 (11.60)	480.00 (139.20)
Total physician visit cost				228.95 (66.40)
Hospitalisation				
	10	1	241.10 (69.92)	24.11 (6.99)
Health system cost (physician visit + hospitalisation)				**253.06 (73.39)**
Patient and family				
Family				
Informal care				
Productivity loss to primary care giver				
Formal sector workers	42	20	8.80 (2.55)	73.92 (21.44)
Informal sector workers	58	24	15.00 (4.35)	208.80 (60.55)
Sub-total				282.72 (81.99)
Total cost of informal care	40	1	282.72 (81.99)	113.09 (32.80)
Travel cost for follow-up	100	0.67	28.98 (8.40)	19.42 (5.63)
Travel cost for OPD visits	40	1	28.98 (8.40)	1.59 (3.36)
Productivity loss to others in family	100	1.17	99.58 (28.88)	116.51 (33.79)
Total family cost				**260.61 (75.58)**
Patient				
Productivity loss to patient due to illness and confinement at home				

Cost item	Percentage treated	Frequency of use	Unit cost (GHC (AUD))	Total cost (GHC (AUD))
Formal sector workers	42	20	8.80 (2.55)	73.92 (21.44)
Informal sector workers	58	24	15.00 (4.35)	208.80 (60.55)
Sub-total				282.72 (81.99)
Total cost due to staying home	40		282.72 (81.99)	113.09 (32.80)
Productivity loss to seeking care	60	0.17	99.58 (28.88)	10.16 (2.95)
Travel cost for follow-up	100	0.17	28.98 (8.40)	4.93 (1.43)
Travel cost for OPD visits	40	1	28.98 (8.40)	11.59 (3.36)
Total Patient cost				139.76 (40.53)
Total patient and family cost				**400.37 (116.11)**
Total societal cost for pre-progression (health system + patient and family)				**653.43 (189.48)**

Abbreviations: AUD: Australian dollars, GHC: Ghana cedis. Exchange rate: 1 GHC is equivalent to 0.29 AUD.

Derivation of costs of progression state is also presented in Table 8-9. The same methodological approach used in estimating cost of progression-free state was used. In this state it was assumed that all patients needed one family member to render informal care. Family caregivers lost up to 24 days per month in care giving. Ten percent (10%) of patients were assumed to be hospitalised once in a month.

Table 8-9: Estimation of costs of progression state

Cost item	Proportion treated	Frequency of use	Unit cost (GHC (AUD))	Total cost (GHC (AUD))
Health system cost				
Physician visits				
Follow-ups with oncologist	100	0.17	26.04 (7.55)	4.43 (1.28)
General laboratory test for follow-ups	100	0.17	41.15 (11.93)	7.00 (2.03)
FBC	100	1	11.74 (3.40)	11.74 (3.40)
LFTs	100	1	16.81 (4.87)	16.81 (4.87)
Kidney function test	100	1	12.60 (3.65)	12.60 (3.65)
OPD visits to treat symptoms	80	1	26.04 (7.55)	20.83 (6.04)
Cost of drugs to treat symptoms	80	1	591.66 (171.58)	473.33 (139.01*)*
Analgesics	100	30	3.65 (1.06)	109.38 (31.72)
Haematinics	40	30	0.19 (0.06)	2.28 (0.66)
Others	40	30	40.00 (11.60)	480.00 (139.20)
Total Physician visits costs				**505.58 (139.20)**
Hospitalisation				
	40	1	241.10 (69.92)	**96.44 (27.97)**
Total health system cost (physician visits + hospitalisation)				**602.02 (174.59)**
Patient and family				
Family				
Informal care				
Productivity loss to primary care giver				
Formal sector workers	42	20	8.80 (2.55)	73.92 (21.44)
Informal sector workers	58	24	15.00 (4.35)	208.80 (60.55)
Total informal care	100	1	282.72 (81.99)	282.72 (81.99)
Travel cost for follow-up	100	0.67	28.98 (8.40)	19.42 (5.63)

Cost item	Proportion treated	Frequency of use	Unit cost (GHC (AUD))	Total cost (GHC (AUD))
Travel cost for OPD visits	80	1	28.98 (8.40)	23.14 (6.71)
Productivity loss of others in family	100	1.17	99.58 (28.88)	116.51 (33.79)
Total Family cost				**441.83 (128.13)**
Patient				
Productivity loss to patient due to illness and confinement at home				
Formal sector workers	42	20	8.80 (2.55)	73.92 (21.44)
Informal sector workers	58	24	15.00 (4.35)	208.80 (60.55)
Sub-total				282.72 (81.99)
Total cost due to staying home	80	1	282.72 (81.99)	226.18 (65.59)
Productivity loss to seeking care	20	0.17	99.58 (28.88)	3.39 (0.98)
Travel cost for follow-up	100	0.17	28.98 (8.40)	4.93 (1.43)
Travel cost for OPD visits	80	1	28.98 (8.40)	23.18 (6.72)
Total patient cost				**257.67 (74.72)**
Total Patient and family costs				***699.50 (202.86)***
Total societal cost for progression (health system cost + patient and family costs)				**1,301.52 (377.44)**

Abbreviations: AUD: Australian dollars, GHC: Ghana cedis. Exchange rate: 1 GHC is equivalent to 0.29 AUD.

Table 8-10 presents a summary of costs estimated for both pre-progression and progression states. The costs due to adverse events of tamoxifen were calculated in the same way as for the health states. Costs incurred by patients and families constituted about one-third of the total costs of treatment to the society.

All costs and effects were discounted at 3% discount rate.

Table 8-10: Summary of costs used in the advanced breast cancer model

Cost centre	Cost (GHC (AUD))
Tamoxifen	36.00 (10.44)
Progression-free state	653.00 (189.49)
Progress state	1,301.52 (377.44)
Initial adverse events	125.87 (36.50)
Ongoing adverse events	3.60 (1.04)

Note: All costs presented are per month and are incurred every month throughout the treatment, with the exception of initial costs of adverse events, which are incurred once when a patient enters the model.
Abbreviations: AUD: Australian dollars, GHC: Ghana cedis.
Exchange rate: 1 GHC is equivalent to 0.29 AUD.

Summary of translational issues

Table 8-11 provides a summary of each translational issue discussed above and their use in the economic model presented in section 8.3.

Table 8-11: Summary of translational issues addressed and their uses in the model

Issues addressed	Results to be used in the model	Cross reference	Results used in sensitivity analysis	Cross reference
Advanced breast cancer				
Applicability of clinical efficacy data – comparison of intervention and patient characteristics between Ghanaian population and source of data used in the model	Economic model is based on efficacy data of clinical trials with characteristics applicable to the Ghanaian population	Section 8.2.3	None	NA
Transformation of the best available data on clinical efficacy data on tamoxifen to derive transition probabilities that suit the Ghanaian context	PFS – 0.010 SAP – 0.025 OS – 0.021	Section 8.2.3	Lower and upper values of 95% CI for transition probabilities	Sections 8.2.4, 8.3.2
Targeted literature search for utility values and their transformation to the health states in the model	PFS – 0.789 PS – 0.569	Section 8.2.3	Lower and upper values of 95% CI for utilities	Sections 8.2.4, 8.3.2
Literature review for disutilities due to adverse events of tamoxifen and expert advice on what to include, frequency and proportion	VB – 0.07 MSD – 0.18 DVT – 0.14 PE – 0.19	Section 8.2.3	Proportions of patients with AEs were varied	Sections 8.2.4, 8.3.2

Abbreviations: AEs; adverse events, CI: confidence interval, DVT: deep vein thrombosis, MSD: musculoskeletal disorders, NA: not applicable, OS: overall survival, PE: pulmonary embolism, PFS: progression-free state, PS: progression state, SAP: survival after progression, VB: vaginal bleeding

8.2.4 Sensitivity analysis

Univariate sensitivity analysis

To assess the strength of the results, a number of parameters were independently tested. These included the utility weights used, transition probabilities, discount rate and costs of each health state. These parameters were varied using the same method employed for the early breast cancer model in Chapter 7, section 7.2.5, with the exception of the averages of utility weights used in economic evaluation studies reviewed in Chapter 6, which were not used in this model. Table 8-12 presents the ranges used in the univariate sensitivity analysis.

Table 8-12: Ranges of parameters used in the univariate sensitivity analysis

Parameter	Base estimate	Range for sensitivity analysis	
		Lower bound	Upper bound
Costs			
Progression-free state	253.06	126.53	379.58
Progression state	602.02	301.01	903.03
Tamoxifen	36.00	18.00	54.00
Adverse events – initial	125.87	62.93	188.80
Adverse events – ongoing	3.60	1.80	5.40
Utilities			
Progression-free state – tamoxifen arm	0.79	0.70	0.89
Progression state – tamoxifen arm	0.57	0.51	0.64
Progression-free state – no tamoxifen arm	0.66	0.60	0.72
Progression state – no tamoxifen arm	0.44	0.39	0.48
Adverse events – initial	-0.04	-0.041	-0.039
Adverse events – ongoing	-0.01	-0.015	-0.010
Transition probabilities			
Progression from progression-free state – tamoxifen arm	0.010	0.009	0.012
Progression from progression-free state – no tamoxifen arm	0.013	0.012	0.015
Breast cancer death from progression-free state – tamoxifen arm	0.021	0.016	0.027
Breast cancer death from progression-free state – no tamoxifen arm	0.027	0.019	0.037
Death from progression state – tamoxifen arm	0.025	0.024	0.027
Death from progression state – no tamoxifen arm	0.032	0.031	0.034
Others			
Discount rate	0.03	0	5, 10
Start age	49	34.3	49
Time horizon	10	5	15

Scenario analysis – Deriving the ICER from the perspective of the society

To account for the costs incurred by patients and family, which constitute a major part of the overall cost of treating advanced breast cancer in Ghana, these costs were included in the costs of treatment. Thus, societal perspective included costs to the health system, patients and family. This was done to provide further information on the impact of these additional costs, and how the perspective of analysis taken for a terminal disease could impact the ICER and decisions made by government.

Scenario analysis – Using the patented and current market price of tamoxifen

This scenario analysis was conducted to account for the impact of the price of tamoxifen when it was first introduced onto the market (under patent) and the current price of tamoxifen on the Ghanaian market. The rationale for this analysis was presented in Chapter 7 section 7.2.5

Scenario analysis – Using transition probabilities from the cohort study only

To test for uncertainties surrounding the choice of efficacy estimates used for this model (that is estimates from an RCT adjusted using the no tamoxifen arm of a cohort study), the overall survival rates reported by Yang et al. (224) in a retrospective cohort study of Korean women were used. As already mentioned in Chapter 6, section 6.5.1, Yang et al. (224) reported only the overall survival rate for the tamoxifen and no tamoxifen arms. Therefore, to use these data to populate the model, it was assumed that the hazard rate for overall survival was the same as the hazard rate for pre-progression state and survival after progression. Monthly transition probabilities were estimated applying the same methods used in the base case analysis.

Scenario analysis – Using life years saved as health outcome

In the same manner carried out for the early breast cancer model, life years saved was used as a health outcome measure in a sensitivity analysis to assess the effect of quality of life on the base case ICER.

Scenario analysis – Using DALYs as health outcome

A scenario analysis was conducted to estimate the effectiveness of tamoxifen for the adjuvant treatment of advanced breast cancer in terms of DALYs averted, that is, the burden of breast cancer without the intervention, tamoxifen. The same methods used to derive the DALYs averted for the early breast cancer model were used[41].

[41] Mortality rates used for the current model was derived from that reported by EBCTG (213).

Table 8-13 presents the DALYs per health state used in the sensitivity analysis. The estimation of DALYs and the DALYs averted per health state are detailed in Appendix 6, Table 11-11.

Table 8-13: DALYs averted per health state

	DALYs averted	
Health state	**Tamoxifen arm**	**No tamoxifen arm**
Pre-progression	0.91	0.91
Progression	0.24	0.00

Abbreviation: DALYs: Disability adjusted life years

Scenario analysis: Noncompliance with tamoxifen treatment regimen

The impact of noncompliance on the effectiveness of tamoxifen was modelled using the same approach reported in the early breast cancer model (Chapter 7 section 7.3.3.11)

Probabilistic sensitivity analysis (PSA)

PSA was conducted to ascertain the uncertainty surrounding the deterministic ICER estimated, for the reasons already enumerated in Chapter 7, section 7.5.5. The uncertainties surrounding the model input parameters were described using the parametric distributions presented in

Table 8-14, with each choice justified. The mean parameter values, assumed parametric distributions and the alpha and beta/lambda parameters used in the PSA are summarised in Table 8-15.

Table 8-14: Parametric distributions used for PSA in the advanced breast cancer model

Type of parameter	Distribution	Justification	Alpha	Beta/ lambda
Monthly transition probabilities	Log-normal	The lower bound of the hazard rates from which they were derived from were zero, and skewed to the right	$In\ (mean)$	$SQRT((In(mean)\|median) \times 2)$
Utilities	Beta	Parameters were far from zero, with lower bound of zero and upper bound of 1	$\frac{mean^2 \times (1-mean)}{SE^2} - mean$	$alpha \times \frac{(1-mean)}{mean}$
Disutilities	-gamma	Parameter is bounded by zero at the upper boundary with no lower bound	$\frac{mean^2}{SE^2}$	$\frac{SE^2}{mean}$

Type of parameter	Distribution	Justification	Alpha	Beta/ lambda
Costs	Gamma	These parameters have zero as lower bound but have no upper bound		

Source: Briggs et al 2003 and TreeAge pro 2017 manual
Abbreviations: SE: standard error

Table 8-15: Model (advanced breast cancer) inputs for PSA

Variable	Value	Distribution	SE	α	β/λ
Transition probabilities					
Probability of progression from progression-free state for tamoxifen	0.010	Log-normal	0.009	-4.561	0.449
Probability of progression from progression-free state for no tamoxifen	0.013	Log-normal	0.012	-4.317	0.395
Probability of breast cancer death from progression-free state for no tamoxifen	0.021	Log-normal	0.020	-3.874	0.314
Probability of breast cancer death from progression-free state for tamoxifen	0.027	Log-normal	0.026	-3.631	0.277
Probability of death from progression state for tamoxifen	0.025	Log-normal	0.024	-3.679	0.284
Probability of death from progression state for no tamoxifen	0.032	Log-normal	0.031	-3.437	0.251
Utilities and disutilities					
Progression-free state – tamoxifen arm	0.79	Beta	0.06	31.18	8.36
Progression state – tamoxifen arm	0.57	Beta	0.06	38.66	29.28
Progression-free state – no tamoxifen arm	0.66	Beta	0.05	72.36	38.19
Progression state– no tamoxifen arm	0.44	Beta	0.05	42.09	54.67
Adverse events – initial*	-0.04	- Gamma	0.02	7.11	177.78
Adverse events – ongoing*	-0.01	- Gamma	0.01	4	400
Costs					
Progression-free state	653.43	Gamma	326.71	4	0.01
Progression state	1,301.52	Gamma	650.76	4	325.38
Tamoxifen	36.00		18.00		0.11
Adverse events – initial	125.87	Gamma	62.93	4	0.03
Adverse events – ongoing	3.60	Gamma	1.80	4	0.11

Note: estimates used in the model were rounded up to five decimal places
Abbreviations: SE: standard error, α: alpha, β: beta (estimated for beta distribution), λ: lambda (estimated for gamma distributions)
*Disutility

8.3 Results

8.3.1 Base case deterministic results

Figure 8-4 presents the Markov trace for the advanced breast cancer model. Five years after model entry, more than one-half of the patients in both treatment arms had died, 66.6% of women on tamoxifen and 75.6% otherwise. Subsequently, by the end of the model cycle, 94.3% of patients on tamoxifen had died, compared to 97.5% of those who were not on tamoxifen treatment. These values were validated through expert opinion on the survival rate of Ghanaian women diagnosed with advanced breast cancer which was similar to that seen in the model; 80% were reported to be dead by five years after diagnosis irrespective of their hormonal receptor status and the treatment received. In addition, the survival rate of patients receiving adjuvant tamoxifen treatment in this model is comparable to that of South African women with breast cancer; 33.4% versus 50%, given that in the former, patients were stage III and 26% of them were not receiving tamoxifen because they were not hormone receptor positive (257).

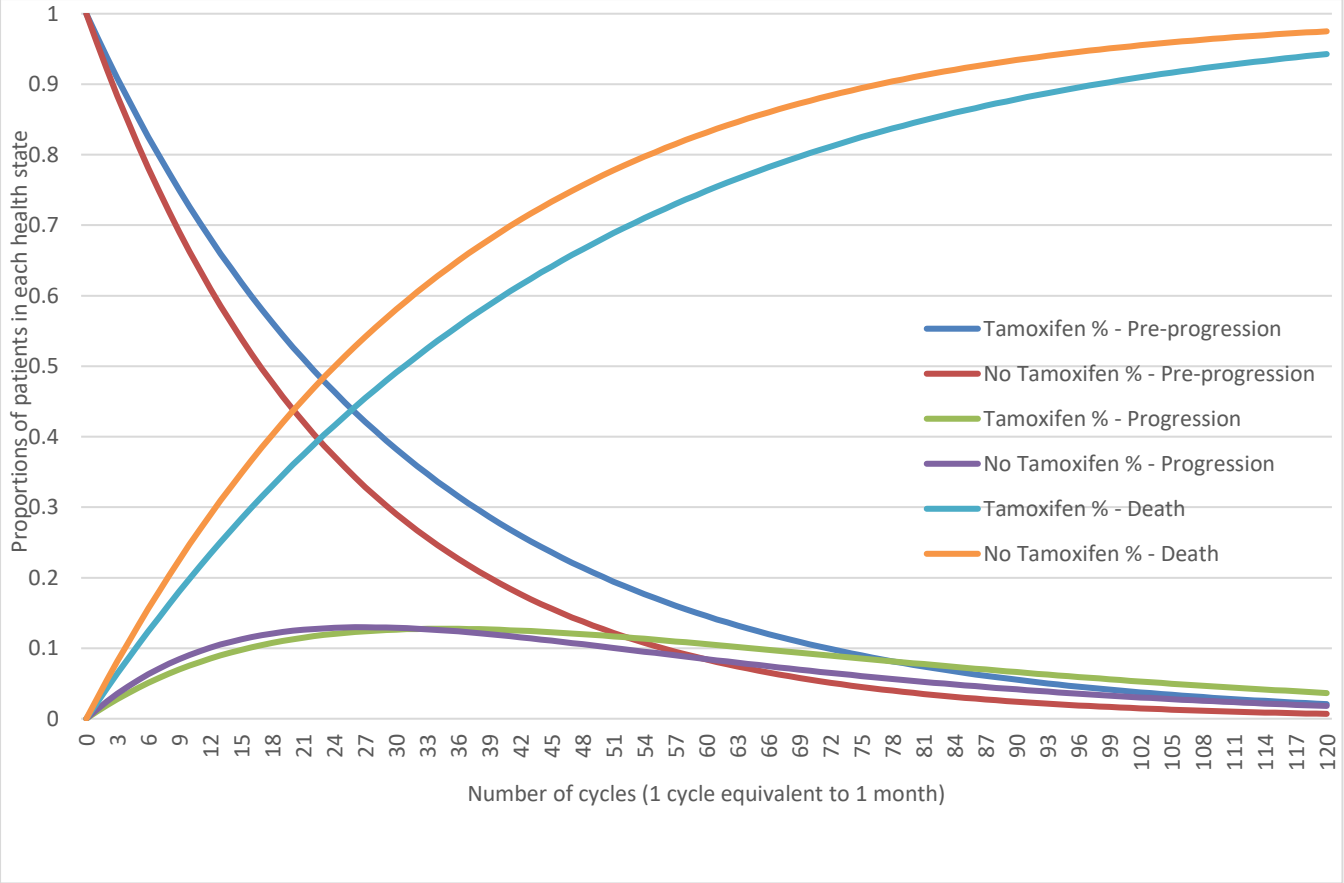


Figure 8-4: Markov trace for advanced breast cancer model

Table 8-16 presents the deterministic results of the model. On average, the cost per patient was GHC 13,936 (AUD 4,041) for those on tamoxifen and GHC 10,531 (AUD 3,054) for those who did not receive tamoxifen. In addition, while patients on tamoxifen gained 2.28 QALYs, those on no tamoxifen gained 1.56 QALYs. Thus, patients on tamoxifen gained 0.76 QALYs at an additional cost of GHC 3,405 (AUD 987). Subsequently, the ICER per patient was estimated as GHC 4,480 (AUD 1,299).

To validate the base case results, the average QALYs gained per patient in the tamoxifen arm was compared to the median survival time reported in the clinical trial, two years nine months. The latter is higher than the former and this could be explained by the differences in the population. The age specific death rates of Ghanaian women are higher compared to those in the trial population, thus women dying from causes other than breast cancer can explain the

lower survival time observed in the model. In addition, the model assumed a constant hazard rate of tamoxifen, which may not have been the case in the clinical trial.

Table 8-16 : Incremental cost effectiveness ratio for base case model

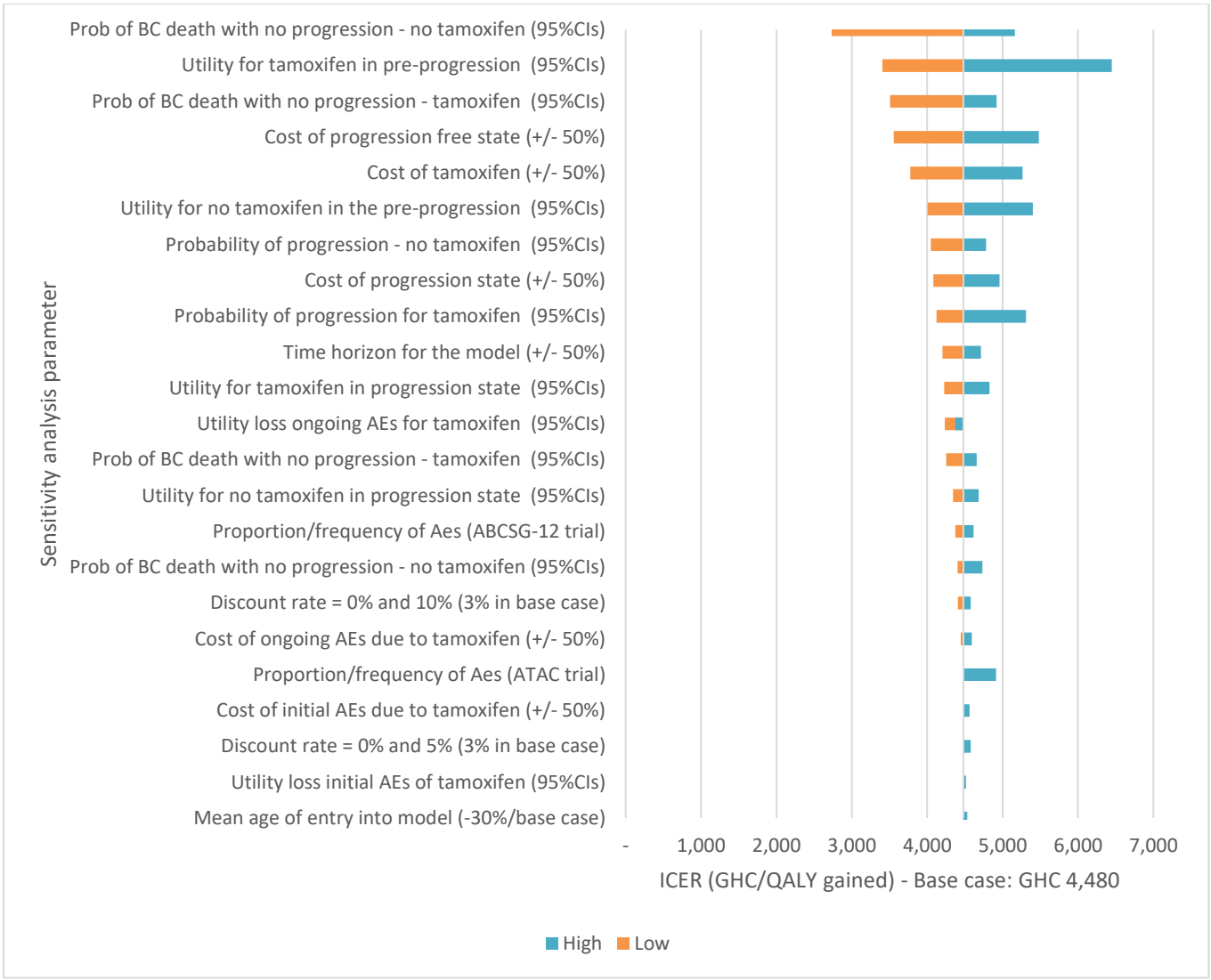
Treatment arm	Cost (GHC (AUD))	Incremental cost (GHC (AUD))	QALYs	QALYs gained	ICER (GHC (AUD))/QALYs gained
No tamoxifen	10,531 (3,054)		1.52		
Tamoxifen	13,936 (4,041)	3,405 (987)	2.28	0.76	4,480 (1,299)

Abbreviations: AUD: Australian dollars, GHC: Ghana cedis, QALYs: quality adjusted life years, ICER: incremental cost effectiveness ratio. Exchange rate: 1 GHC is equivalent to 0.29 AUD.

8.3.2 Sensitivity analysis

Univariate sensitivity analysis

A tornado diagram presents the results of the univariate sensitivity analysis conducted on the base case model when some parameters were varied independently (Figure 8-5). The ICER per analysis is also presented in Table 8-17. The model was most sensitive to adjustments in the probability of death due to breast cancer with no progression for both the tamoxifen and no tamoxifen treatment arms. ICERs were GHC 4,941 (AUD 1,433), GHC 3,504 (AUD 1,016) and GHC 2,751 (AUD798), GHC 5,155 (AUD 1,495) for the lower and upper confidence interval values of the tamoxifen and no tamoxifen arms, respectively. The model was also sensitive to the 50% increase in the cost of pre-progression state; the resulting ICER was 30% higher than the base case – GHC 4,980 (AUD 1,444), but moderately sensitive to the same percentage increase in the costs of tamoxifen and the progression state; 10% and 13% increment in ICER, respectively.



Abbreviations: AEs: adverse events, BC: breast cancer, Prob: probability

Figure 8-5: Tornado diagram for univariate sensitivity analysis of individual parameters

Table 8-17: ICERS for univariate sensitivity analysis of advanced breast cancer model

Sensitivity analysis parameter	Incremental cost (GHC (AUD))	QALYs gained	ICER (GHC (AUD)) /QALY gained
Cost of tamoxifen (-50%)	2,844 (825)	0.75	3,792 (1,100)
Cost of tamoxifen (+50%)	3,965 (1,150)	0.75	5,287 (1,533)
Cost of pre-progression (-50%)	2,680 (777)	0.75	3,573 (1,036)
Cost of pre-progression (+50%)	4,130 (1,198)	0.75	5,506 (1,597)
Cost of progression (-50%)	3,075 (892)	0.75	4,099 (1,189)
Cost of progression (+50%)	3,735 (1,083)	0.75	4,980 (1,444)
Cost of initial AEs (-50%)	3,373 (978)	0.75	4,498 (1,304)
Cost of initial AEs (+50%)	3,436 (997)	0.75	4,582 (1,329)
Cost of ongoing AEs (-50%)	3,350 (971)	0.75	4,466 (1,295)
Cost of ongoing AEs (+50%)	3,460(1,003)	0.75	4,613 (1,338)
Probability of progression from PFS - Tamoxifen (lower CI)	3,183 (923)	0.77	4,134 (1,199)

Sensitivity analysis parameter	Incremental cost (GHC (AUD))	QALYs gained	ICER (GHC (AUD)) /QALY gained
Probability of progression from PFS - Tamoxifen (upper CI)	3,816 (1,107)	0.72	5,300 (1,537)
Probability of progression from PFS - No tamoxifen (lower CI)	3,547 (1,029)	0.74	4,794 (1,390)
Probability of progression from PFS - No tamoxifen (upper CI)	3,137 (910)	0.78	4,022 (1,166)
Probability of death due to breast cancer from PFS - Tamoxifen (lower CI)	5,435 (1,576)	1.1	4,941 (1,433)
*Probability of death due to breast cancer from PFS - Tamoxifen (upper CI)	1,507 (437)	0.43	3,504 (1,016)
*Probability of death due to breast cancer from PFS - No tamoxifen (lower CI)	1,156 (335)	0.42	2,751 (798)
Probability of death due to breast cancer from PFS - No tamoxifen (upper CI)	5,361(1,555)	1.04	5,155 (1,495)
Probability of death due to breast cancer from progression - Tamoxifen (lower CI)	3,564 (1,034)	0.77	4,629 (1,342)
Probability of death due to breast cancer from progression - Tamoxifen (upper CI)	3,108 (901)	0.73	4,258 (1,235)
Probability of death due to breast cancer from progression - No tamoxifen (lower CI)	3,284 (952)	0.75	4,378 (1,270)
Probability of death due to breast cancer from progression - No tamoxifen (upper CI)	3,632 (1,053)	0.77	4,716 (1,368)
Utility loss for progression-free state - Tamoxifen (lower CI)	3,405 (987)	0.53	6,424 (1,863)
Utility loss for progression-free state - Tamoxifen (upper CI)	3,405 (987)	1.00	3,405 (987)
Utility loss for progression-free state - No tamoxifen (lower CI)	3,405 (987)	0.85	4,006 (1,162)
Utility loss for progression-free state - No tamoxifen (upper CI)	3,405 (987)	0.63	5,404 (1,567)
Utility loss for progression state - Tamoxifen (lower CI)	3,405 (987)	0.71	4,795 (1,391)
Utility loss for progression state - Tamoxifen (upper CI)	3,405 (987)	0.81	4,203 (1,219)
Utility loss for progression state - No tamoxifen (lower CI)	3,405 (987)	0.78	4,365 (1,266)
Utility loss for progression state - No tamoxifen (upper CI)	3,405 (987)	0.73	4,664 (1,353)
Utility loss for initial AEs (no utility loss - 0)	3,405 (987)	0.76	4,480 (1,299)
Utility loss for ongoing AEs (no utility loss - 0)	3,405 (987)	0.78	4,365 (1,266)
Discount rate (0%)	3,834 (1,112)	0.84	4,564 (1,324)
Discount rate (5%)	3,162 (917)	0.71	4,454 (1,292)
Discount rate (10%)	2,671 (775)	0.61	4,379 (1,270)
Time horizon (-50%)	2,319 (672)	0.55	4,216 (1,223)
Time horizon (+50%)	3,772 (1,094)	0.8	4,715 (1,367)
Proportion/frequency of adverse events (ABCSG-12 trial)	3,415.88 (990.61)	0.75	4,533.81(1,314.80)
Proportion/frequency of adverse events (ATAC trial)	3,566.40 (1,034.26)	0.75	4,733.57 (1,372.74)

Abbreviations: AEs: adverse events, AUD: Australian dollars, GHC: Ghana cedis, CI: confidence interval, QALY: quality adjusted life years, ICER: incremental cost effectiveness ratio. Exchange rate: 1 GHC is equivalent to 0.29 AUD.

*ICER is most sensitive to parameter.

Scenario analysis – Deriving the ICER from the perspective of the society

Table 8-18 presents the ICER from the perspective of the society. The incremental cost and ICER derived were 47% higher than the base case scenario: GHC 6,466 (AUD 1,875) and GHC 8,508 (AUD 2,467) respectively. This indicates that unlike the early breast cancer model, costs incurred by patients and their families are key drivers of the ICER for the advanced breast cancer model.

Table 8-18: Incremental cost effectiveness ratio derived from health system's perspective

Treatment arm	Cost (GHC (AUD))	Incremental cost (GHC (AUD))	QALYs	QALYs gained	ICER (GHC (AUD))/QALYs gained
No tamoxifen	25,186 (7,304)		1.56		
Tamoxifen	31,652 (9,179)	6,466 (1,875)	2.28	0.76	8,508 (2,467)

Abbreviations: AUD: Australian dollars, GHC: Ghana cedis, QALYs: quality adjusted life years, ICER: incremental cost effectiveness ratio. Exchange rate: 1 GHC is equivalent to 0.29 AUD.

Scenario analysis – Using the patented and current market price of tamoxifen

The ICER when the patented and current market price of tamoxifen were used was GHC 36,033 (AUD 10,450) (8 times the base ICER) and GHC 5,463 (AUD 1,584) (22% more than the base case) respectively as shown in Table 8-19.

Table 8-19: ICER using the patented and market price of tamoxifen

Sensitivity analysis parameter	Incremental cost (GHC (AUD))	QALYs gained	ICER (GHC (AUD)) /QALY gained
Patented price of tamoxifen	27,385 (7,942)	0.76	36,033 (10,450)
Current market price of tamoxifen	4,152 (1,204)	0.76	5,463 (1,584)

Abbreviations: AUD: Australian dollars, GHC: Ghana cedis, QALYs: quality adjusted life years, ICER: incremental cost effectiveness ratio. Exchange rate: 1 GHC is equivalent to 0.29 AUD.

Scenario analysis – Using transition probabilities from the cohort study only

When the transition probabilities from the cohort study were used to populate the model, approximately 8% of patients in the tamoxifen arm were alive at the end of the model cycle

compared to 2% in the base case. In addition, for the tamoxifen arm, 74% of patients were dead at the end of 10 years compared to 94% in the base case. Figure 8-6 presents the Markov trace under this scenario.

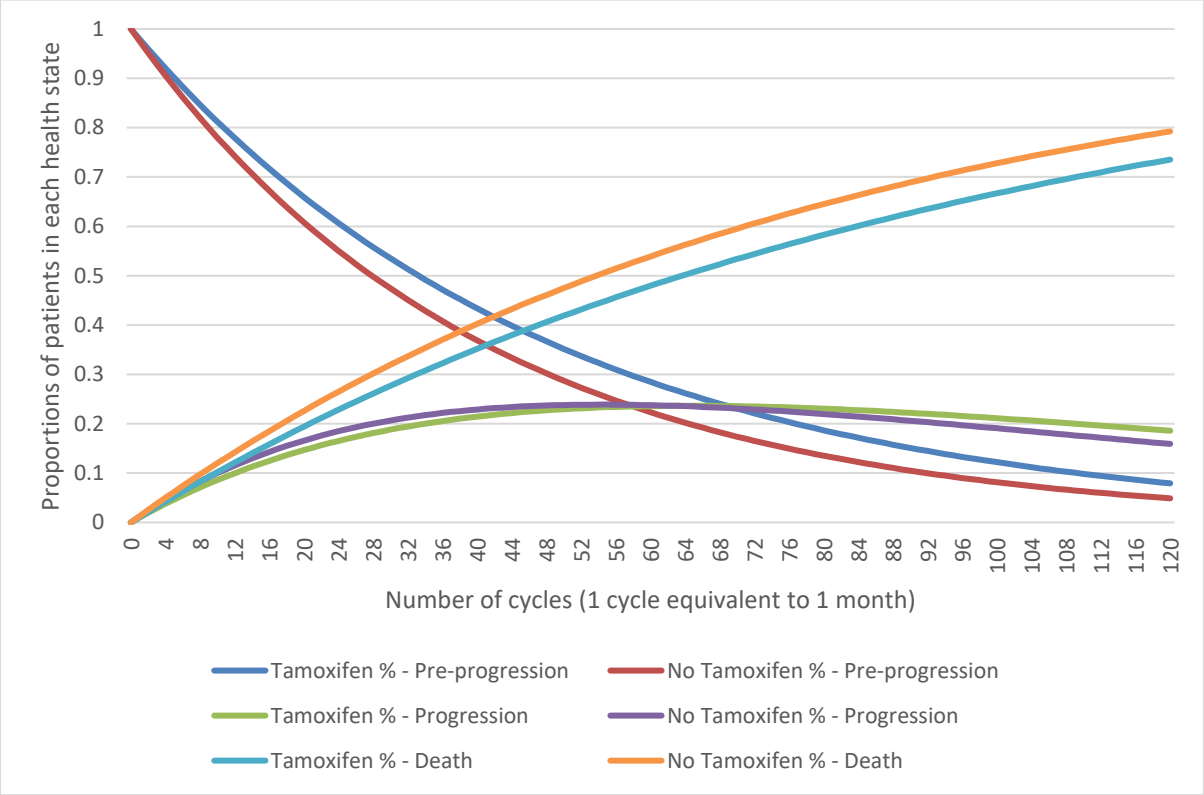


Figure 8-6: Markov trace when transition probabilities from cohort study alone was used

Table 8-20 presents the ICER calculated using transition probabilities derived from the cohort study. In this scenario, patients on tamoxifen treatment gained more QALYs at a lower incremental cost compared to the base case: 0.92 QALYs at an incremental cost of GHC 2,967 (AUD 860) versus 0.76 QALYs at an incremental cost of GHC 3,405 (AUD 987). The rise in the incremental cost is due to more patients surviving and as such using more resources. Consequently, the ICER estimated was approximately 28% less than the base case ICER: GHC 3,225 (AUD 935) versus GHC 4,480 (AUD 1,299).

Table 8-20: ICER estimated using transition probabilities derived from cohort study

Treatment arm	Cost (GHC (AUD))	Incremental cost (GHC (AUD))	QALYs	QALYs gained	ICER (GHC (AUD))/QALYs gained
No tamoxifen	20,696 (6,002)		2.62		
Tamoxifen	23,663 (6,862)	2,967 (860)	3.54	0.92	3,225 (935)

Abbreviations: AUD: Australian dollars, GHC: Ghana cedis, QALYs: quality adjusted life years, ICER; incremental cost effectiveness ratio. Exchange rate: 1 GHC is equivalent to 0.29 AUD.

Scenario analysis – Using life years saved as health outcome

Table 8-21 presents a comparison of incremental benefits and ICERs for two different measures of health outcomes: life years and QALYs. Similar to the early breast cancer model, life years saved were lower than QALYs gained even though a patient gained more life years on the average compared to QALYs in both treatment arms. Evidently, quality of life of patients has to be driving the incremental benefit, and consequently the ICER. The ICER per life years saved was GHC 5,973 (AUD 1,732).

Table 8-21: Comparison of ICERS using QALYs and life years saved as health outcome

Treatment arm	Costs		Life years			QALYs		
	Cost (GHC (AUD))	Incremental cost (GHC (AUD))	LY	LYG	ICER (GHC (AUD))/ LYG	QALYs	QALYs gained	ICER (GHC (AUD))/QALYs gained
No tamoxifen	10,531 (3,054)		2.56			1.56		
Tamoxifen	13,936 (4,041)	3,405 (987)	3.13	0.57	5,973 (1,732)	2.28	0.76	4,480 (1,299)

Abbreviations: AUD: Australian dollars, GHC: Ghana cedis, LY: life years, LYG: life years gained, ICER: incremental cost effectiveness ratio, QALY: quality adjusted life years.
Exchange rate: 1 GHC is equivalent to AUD 0.29.

Scenario analysis – Using DALYs as health outcome

Table 8-22 presents the ICER using DALYs averted as the outcome measure for treating this cohort of women: GHC 5,582 (AUD 1,619), 25% more than the base case result. The

incremental DALYs averted using tamoxifen for treating a pre-and peri-menopausal woman with advanced breast cancer was 0.61 less than the QALYs gained (0.76).

Table 8-22: Incremental cost effectiveness ratio using DALYs averted as health outcome

Treatment arm	Cost (GHC (AUD))	Incremental cost (GHC (AUD))	DALYs averted	Incremental DALYs averted	ICER (GHC (AUD))/DALYs averted
No tamoxifen	10,531 (3,054)		1.73		
Tamoxifen	13,936 (4,041)	3,405 (987)	2.34	0.61	5,582 (1,619)

Abbreviations: AUD: Australian dollars, GHC: Ghana cedis, DALYs: Disability adjusted life years, ICER: incremental cost effectiveness ratio. Exchange rate: 1 GHC is equivalent to AUD 0.29.

Scenario analysis: Noncompliance to tamoxifen treatment regimen

Table 8-23 presents the ICER when noncompliance with the treatment regimen of tamoxifen was factored into the model. The higher the reduction in the effectiveness of tamoxifen due to noncompliance, the lower the QALYs gained, and consequently, the higher the ICER, compared to the base case.

Table 8-23: ICER for noncompliance to tamoxifen treatment regimen

Percentage reduction in benefit of tamoxifen	Incremental cost (GHC (AUD))	QALYs gained	ICER (GHC (AUD)) /QALY gained
32% reduction	859 (249)	0.29	2,641 (766)
16% reduction	2,030 (589)	0.50	2,080 (603)
5% reduction	2,952 (856)	0.67	1,805 (523)

Abbreviations: AUD: Australian dollars, GHC: Ghana cedis, ICER: incremental cost effectiveness ratio, QALY: Quality Adjusted Life Years. Exchange rate: 1 GHC is equivalent to AUD 0.29.

Probabilistic sensitivity analysis (PSA)

Figure 8-7 and Figure 8-8 present the PSA results, the cost effectiveness acceptability curve and incremental cost effectiveness scatter plot respectively. At a WTP of GHC 4,337 (AUD 1,258), given the data available, the probability that tamoxifen is cost effective compared to no tamoxifen is 0.51. When the threshold is recalculated using the GDP per capita for year 2017, the probability that tamoxifen is cost effective compared to no tamoxifen is 0.46 at a WTP of

GHC 3,843 (AUD 1,114). As expected, under greater incremental costs, tamoxifen treatment becomes less cost effective when evaluated from the perspective of the society: a probability of 0.33 at WTP of GHC 4,337 (AUD 1,258) and 0.31 at a WTP of GHC 3,843 (AUD 1,114). Thus, tamoxifen is unlikely to be cost effective from the societal perspective.

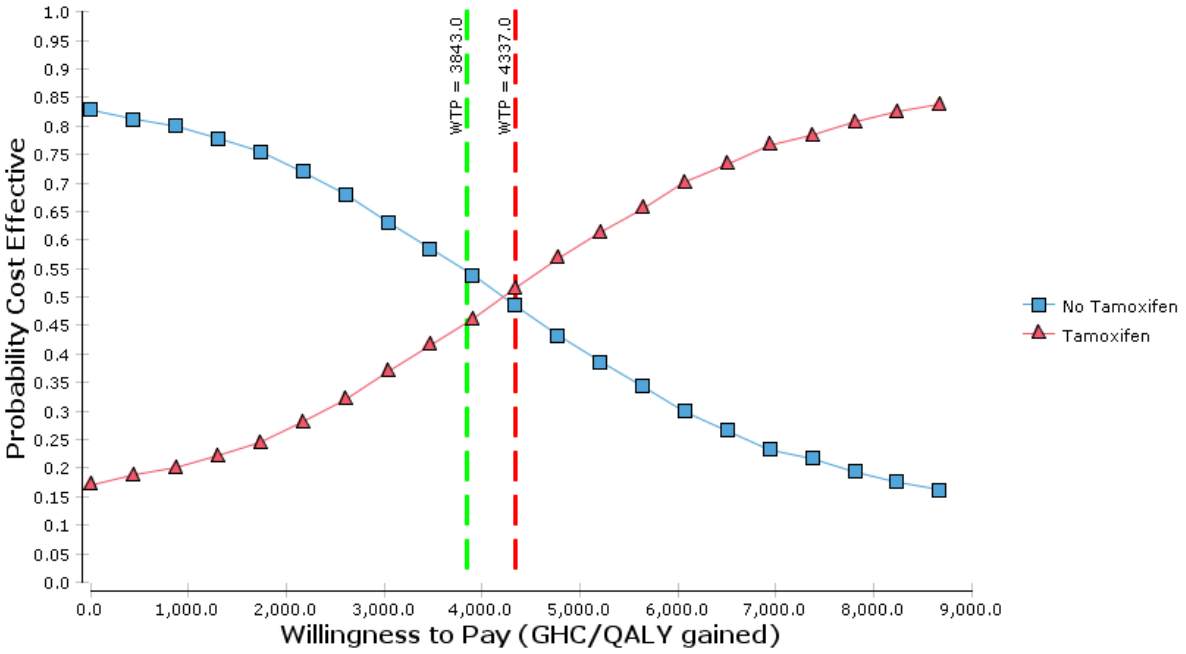
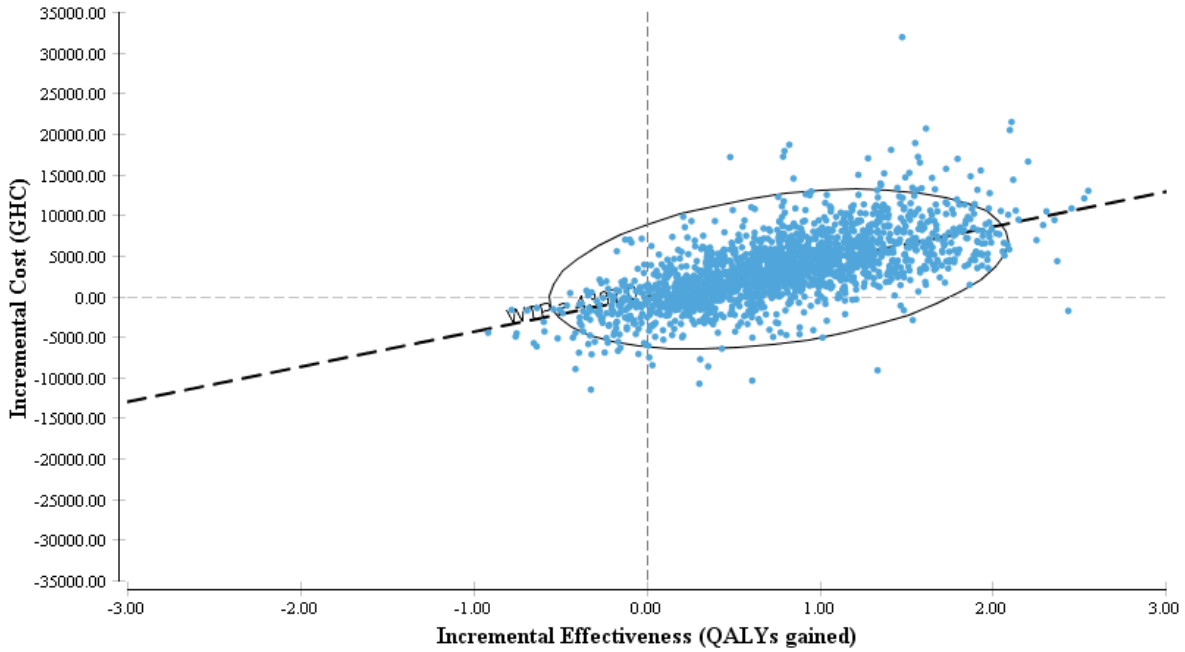


Figure 8-7: Cost effectiveness acceptability curve for the advanced breast cancer model



Source: Calculated in TreeAge using 2,000 simulations

Figure 8-8: Scatter plot for the ICER of the advanced breast cancer model

The ICERs for the deterministic and the probabilistic results are similar (Table 8-24).

Table 8-24: Deterministic versus probabilistic ICERs for – advanced breast cancer model

Type of result	Incremental cost (GHC (AUD))	QALYs gained	ICER (GHC (AUD))/ QALY gained
Deterministic result	3,405 (987)	0.76	4,480 (1,299)
PSA result, mean	3,418 (991)	0.76	4,498 (1,304)
PSA results, median	3,280 (951)	0.75	4,374 (1,268)

Abbreviations: AUD: Australian dollars, GHC: Ghana cedis, QALYs: Quality adjusted life years, ICER: incremental cost effectiveness ratio. Exchange rate: 1 GHC is equivalent to 0.29 AUD.

8.4 Discussion

8.4.1 Summary of major findings

The results of the model show that a pre- or peri-menopausal woman diagnosed with advanced breast cancer gains an additional 0.76 QALYs at an extra cost of GHC 3,405 (AUD 987), when she receives tamoxifen for five years, compared to one who does not. At a WTP of GHC 4,336 (AUD 1,258), the probability that tamoxifen was cost effective compared to no tamoxifen at the estimated ICER, GHC 4,480 (AUD 1,299), was 0.51.

The ICER was sensitive to the probability of death with no progression for both treatment arms and the cost of tamoxifen. Similar to findings for the early breast cancer model (Chapter 7), tamoxifen was not found to be cost effective at the original adjusted patented price. The choice of health outcome measure and compliance with the tamoxifen treatment regimen had an impact on the ICER as seen in the early breast cancer model and in the same direction.

The perspective of the analysis had a major impact on the ICER, unlike the early breast cancer model. The difference is attributed to lower productivity among patients and families in instances where a condition is terminal, such as in the case of advanced breast cancer. From the societal perspective, tamoxifen for the treatment of advanced breast cancer was unlikely to be cost effective.

8.4.2 Comparison with Yang et al. 2010

The current study used a Markov model to synthesise the available data. The clinical effectiveness data used in this study was derived using a non-direct comparison method: the effectiveness of tamoxifen was obtained from an RCT and that of no tamoxifen from both an RCT and a cohort study. The cohort study is the same as that used by Yang et al. (224). Thus, the main difference between the two studies is the fact that this study used an additional source of data, an RCT, which is deemed to provide stronger evidence than a cohort study. Other differences are in the characteristics of patients included in the model (stage of breast cancer), year of estimation and effectiveness outcome, thus these studies are not entirely comparable.

While the current study used QALY weights derived from the coefficients of a meta-regression analysis of 117 health state utility values, taking into account the country specific epidemiology as the measure of health outcome, Yang et al. used life years gained. An advantage of QALYs over life years gained is that they take into account both quality and quantity of life. When life years was used in a sensitivity analysis for the current study, the ICER estimated was higher

than the base case due to a decrease in the incremental benefit, indicating the effect of quality of life on the ICER.

Subsequently, there was a large discrepancy between the ICERs estimated by both studies: GHC 4,480 (AUD 1,299) and GHC 8,508 (AUD 2,467) for health system and societal perspectives respectively in the present study and approximately GHC 2,358 (AUD 684) for Yang et al. The majority of the variations seen in the ICERs could be attributed to the differences mentioned above. However, when the cohort study was used as the only source of effectiveness of tamoxifen, the ICER was less than the base case: GHC 3,225 (AUD 935), further strengthening the differences seen in the ICERs of this study and that of Yang et al.

Another parameter that contributed to the differences in ICERs that is worth mentioning is the costs associated with the different stages of breast cancer. For example, family and patient costs (especially productivity loss) due to stage IV cancer is expected to be more than that associated with stage III.

8.4.3 Strength of the evaluation

This study evaluated the cost effectiveness of tamoxifen for the treatment of advanced breast cancer in pre- and peri-menopausal women using data transformed to be applicable to the Ghanaian context. Resource use and unit costs were local, derived from Ghanaian specific information. Utility weights for each health state were estimated from a meta-regression analysis taking into account the epidemiology of breast cancer in Ghana.

The present study also used DALYs averted as a health outcome measure in a sensitivity analysis, thus providing evidence on the burden of breast cancer as commonly recognised in developing countries such as Ghana.

8.4.4 Key limitations of the evaluation

In addition to some key limitations mentioned in the early breast cancer model (Chapter 7) concerning reliance on Ghanaian clinical experts for defining resource use and the estimation of their associated costs, heterogeneity due to age, and the chosen adverse events and their frequencies, another major limitation of this evaluation is the fact that the ideal data does not exist.

The advanced breast cancer model relied on effectiveness evidence from a RCT and cohort study, in a non-direct comparison method (RCT being the primary source). The methods used in transforming the efficacy data for use in the model are limited by the fact that the two studies had different characteristics, in particular, the composition of the study population. This method was further limited by the assumption that transitions between states were exponential and the overall survival rate of patients in the no tamoxifen arm was the same as the rate at which they progressed from the stable/responsive disease state to the progression state. Not all these assumptions reflect what happens in the real world. Nonetheless, this was the best data available for the model considering the technology under assessment, the diseases' epidemiology and the Ghanaian breast cancer clinical management algorithm. To address these challenges in the future, it may be necessary that the EBCTCG not only focus on aggregating RCT data for the treatment of early breast cancer only, but also synthesis RCT data for the treatment of advanced breast cancer where incidence and prevalence rate are most common in developing countries, where such data is limited.

To identify any source of bias associated with the RCT compared to the cohort study, a sensitivity analysis was conducted using the efficacy estimates of only the cohort study for both treatment arms. This resulted in a lower ICER (28% less) than the base case result. The most plausible explanation of this is that the clinical characteristics of the patients in the cohort study were very different from those in the RCT. In particular, participants in the cohort study

were all in stage III of the disease, while those in the RCT were predominantly in stage IV (94%), meaning that cohort study women had better survival rates. As discussed previously, the proportions of women with stage III and stage IV advanced breast cancer in Ghana are similar to those reported in the RCT. Consequently, the cohort study was rejected because it lacked external validity.

In addition, the estimated ICER may not be a true reflection of what may be observed in real world practice. The model did not factor in a noncompliance rate, which is anticipated to be higher among these women due to the severity of their disease and its associated complications. In a sensitivity analysis, modelling noncompliance resulted in a decrease in QALYs gained and a higher ICER. It demonstrated that impact of noncompliance on the ICER is dependent on the proportion of noncompliant women, the intensity of noncompliance and their overall impact on the benefit of tamoxifen (that is, the percentage reduction in benefit). In addition, as with all models, any assumptions contribute to the uncertainties in the estimated results. However, these were addressed by conducting a sensitivity analysis to assess the effect on the ICER of these assumptions and all parameters used.

8.4.5 Key issues with translation of data to the Ghanaian context for economic evaluation and its implications on HTA conduct in Ghana

To add to the data translation issues and the implication of findings to HTA in Ghana mentioned in Chapter 7 section 7.4.5, the key implication of this evaluation on HTA in Ghana is the importance of choosing an appropriate perspective to conduct economic evaluations in Ghana. Although HTA appraisals are targeted to the payer, hence exclusion of patient and family cost (for example as seen in Australia for PBAC (117)), the same is not applicable in Ghana for all health technologies. The societal perspective will have to be undertaken in an evaluation based on the characteristics of the health technology. For example, in instances of terminal diseases where the Ghanaian health system does not make provisions for most of the care needed

(palliative care in this case), costs are borne by patients and families and should be included in the evaluation. This is important as this evaluation demonstrated the lower productivity of patients and families, and subsequently an impact on the ICER, which decreased the probability that the intervention would be cost effective.

For that reason, it may be pertinent that economic evaluations conducted in Ghana to be undertaken from both a payer and societal perspective, with the base case chosen depending on the characteristics of the health technology. Societal cost includes out of pocket costs and productivity losses to the patients and families and consequently to the government, hence are relevant to the government. Presenting both perspectives provides the decision maker with information on the impact of patient and family costs and productivity losses on the ICER and the probability that the intervention would be worth funding.

Differences in health system characteristics such as the presence or absence of particular services (for example palliative care) further constrains the transferability of economic models from other settings to Ghana. This is indicative of the need to conduct country specific evaluations.

In transferring clinical efficacy data from one setting to the other (especially from a developed to a developing country), an evaluator would have to consider factors other than that recommended by the ISPOR guideline on good research practice for transferability of economic evaluations across jurisdictions (246). These include trial patient characteristics, clinical practice, type of treatment and characteristics of the trial, and should be considered in the choice of trial from which to obtain efficacy data. In the considering these factors, an evaluator will have to make an objective decision on which of these factors to prioritise over the other.

For instance, in this thesis, two studies, one of which was an RCT and the other, a cohort study were identified as plausible sources of clinical efficacy data. Both studies had similar characteristics, and were conducted in different settings, all of which were high-income countries. Hence, in selecting which was most suited and applicable to the Ghanaian population, the rigour of the study and the stage of breast cancer presentation was prioritised. This was because, for breast cancer, the stage of breast cancer presentation is a major indicator of the type of treatment given, which consequently affects the overall budget impact on the health budget. In Ghana, most women, including premenopausal (study population) present at the late stage of breast cancer, hence stage at presentation was deemed as the most important factor to consider in choosing the most appropriate study as source of clinical efficacy data for the evaluation. However, it is recommended that a sensitivity analysis is conducted using the other plausible sources of data, as carried out in this thesis. This will ensure that the robustness of the source of data that was chosen over the others are assessed. In addition, it will present the decision maker with information on how the ICER can be impacted by those other sources of data that were deemed applicable but were not chosen for the evaluation. Therefore, the thesis recommends that the guidelines for transferability of economic evaluations across jurisdictions be updated to reflect some of these additional challenges that may be encountered when addressing transferability issues in decision-analytic models.

That said, it is important to note that other factors such as unreported characteristics of patients or aspects of the health system that can influence the effectiveness of an intervention may not be reported in clinical trial data. Hence, an evaluator is unable to assess objectively such factors for consideration when transferring data across jurisdictions.

8.5 Conclusion

This chapter presented a cost utility analysis of tamoxifen for the adjuvant treatment of advanced breast cancer: there was a 50% probability of cost effectiveness at a WTP of GHC 4,337 (AUD 1,258). Despite a number of limitations, the study has demonstrated that different levels of evidence on clinical effectiveness data which may not be directly related to the comparators under evaluation can be synthesised and transformed into a country specific context for use in an economic evaluation. These limitations can be addressed to an extent in a sensitivity analysis on key model parameters. Nevertheless, it is prudent that measures are put in place to address these challenges in the short- to medium- term. For example, Ghanaian agencies would have to collect and make data easily accessible by researchers. Beyond Ghana, collaborative groups such as the EBCTCG could aggregate RCT data available on advanced breast cancer and other conditions for their use in evaluations and HTA in developing countries. The next chapter presents the financial implications of funding tamoxifen under the Ghana NHIS.

9 HTA IN GHANA: BUDGET IMPACT ANALYSIS OF TAMOXIFEN FOR THE HORMONAL TREATMENT OF BREAST CANCER AMONG PRE- AND PERI-MENOPAUSAL WOMEN

9.1 Introduction

This chapter provides information for decision makers regarding the affordability of tamoxifen and the financial implications of subsidising it on the overall health budget. This chapter presents a budget impact analysis of reimbursing tamoxifen under the NHIS of Ghana. Even though tamoxifen is already reimbursed under the NHIS, the results from the BIA will provide information for the purposes of both present and future planning on how much its funding impacts the NHIS budget.

The BIA undertaken here follows the ISPOR guidelines (102). Section 9.2 presents the methods used and measures taken to ascertain the strength of the parameters used for the BIA. Section 9.3 provides the results from the base case and sensitivity analysis. The findings are interpreted and discussed in section 9.4, highlighting the implications of the BIA for future studies and policy. The major findings of the chapter are summarised in section five.

9.2 Methods

The model for the BIA was developed in Microsoft Excel 2010 and complied with recommended guidelines by the ISPOR task force on the principles of good practice for budget impact analysis report II (102). An epidemiological approach was used to estimate the financial implications of funding tamoxifen for the HTBC in the Ghanaian health system. This approach takes into account the epidemiology of the disease under investigation, its natural history and the resources involved. The analysis was conducted from the perspective of the NHIS (government) and over a five-year time horizon. Costs included in the analysis were

undiscounted because in a BIA the intent is to provide the budget holder with the actual costs to be paid.

9.2.1 Epidemiology

Population

The target population for the BIA is pre- and peri-menopausal women with hormone receptor positive breast cancer in Ghana. It was assumed that women aged between 15 and 50 years were pre- and peri-menopausal women at risk of developing breast cancer. The age range was chosen based on Ghanaian studies that reported the incidence and mortality of breast cancer among the population (205, 210, 211, 284). The population size of interest was sourced from the 2010 Ghana census report, which was projected to 2018 and subsequent years thereafter using the reported population growth rate of Ghana (285). The number of pre- and peri-menopausal women at risk of breast cancer was calculated as 39,977,332 for the five-year period, approximately 8 million per year.

Prevalence of disease

The number of women expected to use tamoxifen for the HTBC was derived using a prevalence-based approach where the number of women (survivors) presenting at a facility over a period with a particular disease is used to estimate the prevalence rate of the disease. Ghana does not have a cancer registry, therefore the administrative data of the KATH oncology centre was used to estimate the prevalence rate of breast cancer in Ghana.

The KATH oncology centre is one of the only two health facilities that provide oncology services in Ghana. The centre serves more than half of the population of Ghana due to its central location in the country, serving nine out of the ten regions (286, 287). Hence, the prevalence rate estimated from the KATH oncology centre registry is representative of the cases of breast cancer seen at KATH and the other facility; Korle Bu Teaching Hospital, and can be

generalised to the entire country. The centre keeps a record of patients who present with breast cancer and are treated there. The record includes the type of cancer, patient demographic characteristics, histopathology results, pathology report to confirm cancer, deaths and number lost to follow-ups. A limitation of using administrative data is its inability to capture persons with the condition who do not use hospital-based services.

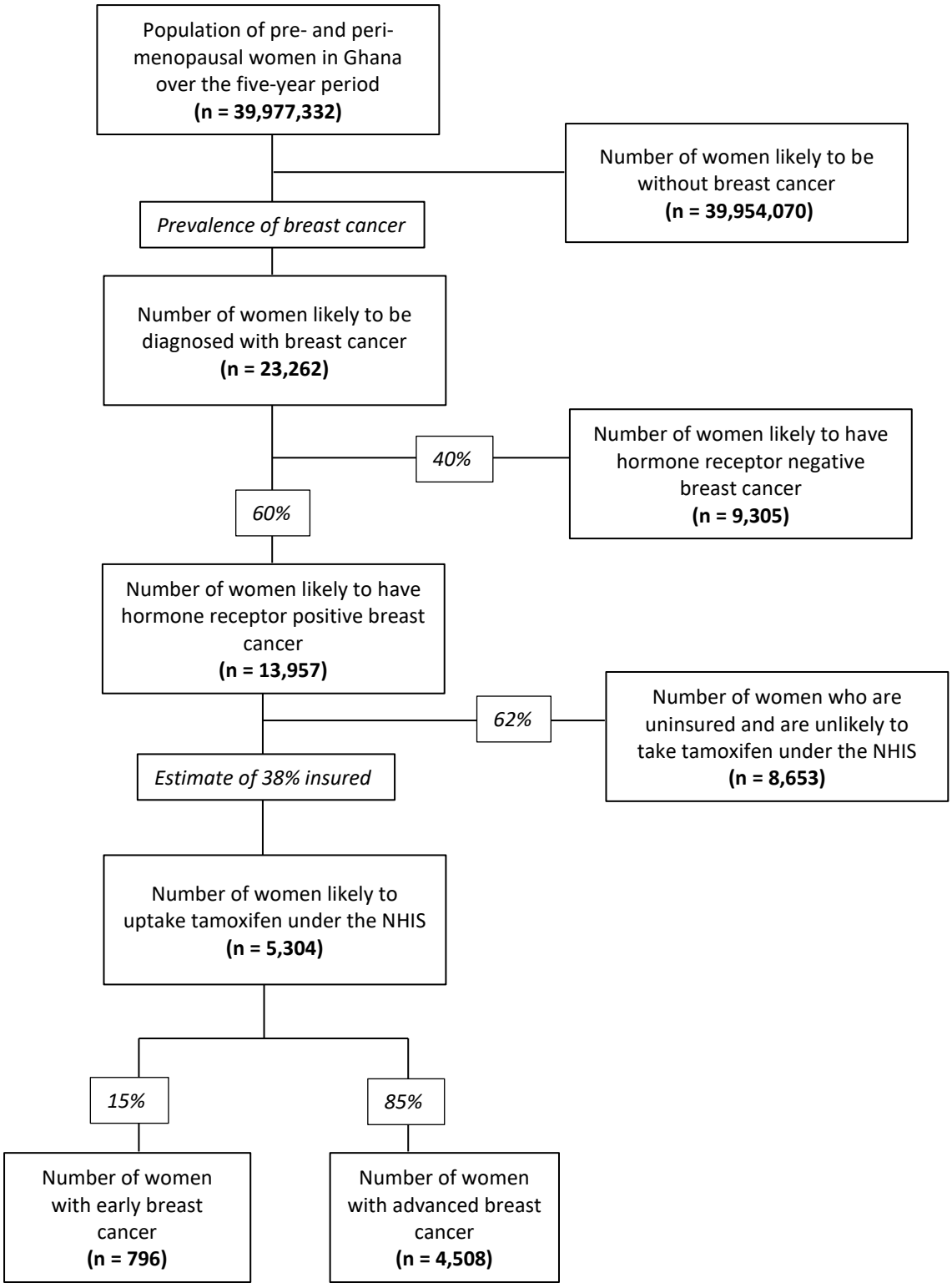
The prevalence rate was estimated using the data available over an eight-year period (2006 to 2013). It was calculated using the count method, where the prevalence of a disease is estimated by dividing the estimated number of survivors for a certain period by the population size (288). The prevalence rate was estimated as 58 per 100,000 women. Subsequently, 23,262 women were calculated as those likely to have breast cancer for the five-year period, approximately 4,600 women per year.

An alternative source of data for the prevalence rate of breast cancer in Ghana is that estimated by the Global Observatory of Cancer (GLOBOCAN) project, as part of the WHO GCO. This was not chosen for the base case analysis because the data that was used to derive the prevalence rate was of poor quality. GLOBOCAN reported that due to the lack of accurate country specific data for Ghana, they derived their prevalence rate from the average incidence rates of a selected number of neighbouring countries (202). The estimated incidence and prevalence rates reported by GLOBOCAN were for all women with breast cancer irrespective of their menopausal status. Prevalence rates were reported per year. Subsequently, the prevalence rates estimated for the study period were 113, 130, 148, 165 and 182 per 100,000 population for years one, two, three, four and five respectively. The influence of the GLOBOCAN prevalence rate on the net cost of tamoxifen to the NHIS was examined in a sensitivity analysis.

9.2.2 Uptake/Utilisation of tamoxifen

To estimate the financial impact of tamoxifen for the budget holder, the target population was placed in two categories: those insured under the NHIS, and the uninsured. The focus of this BIA was to estimate the financial implications of tamoxifen uptake by women who are insured under the NHIS. Women who are not insured pay out of pocket to access care. A secondary analysis estimated the financial implications for the NHIS assuming all women were insured. For the purposes of this analysis, insured patients were further categorised into those with early breast cancer and those with advanced breast cancer.

Figure 9-1 presents the analytical framework of the BIA for the entire population of women likely to receive tamoxifen for a five-year period under the NHIS. The prevalence rate of breast cancer was assumed to be constant over the time horizon. However, the number of patients per year (that is the prevalence per year) increased each year due to the growth in population over the years, hence the increase in numbers estimated for each year.



The numbers presented are the total number of patients for the five-year period used for the analysis.

Figure 9-1: Analytical framework used to derive the target population for the BIA

Women diagnosed with breast cancer in Ghana are investigated for the hormone receptor (HR) status of the breast cancer cells to inform hormonal treatment. Approximately 60% of women diagnosed with breast cancer in Ghana are reported to have HR positive cells (205). Ohene-Yeboah and Adjei (205) established the HR status of breast cancer cells through a retrospective analysis of biopsies taken from breast lumps that had been confirmed as cancerous in a histopathological investigation. Using this evidence, 13,957 women diagnosed with breast cancer were assumed HR positive over the time horizon. The remaining 40% (n = 9,305) were assumed to be those diagnosed with HR negative breast cancers, hence would not be prescribed tamoxifen. Subsequently, the number of women likely to utilise tamoxifen under the NHIS was derived by assuming that all 38% (n=5,304) of those with HR positive breast cancer would be insured by the NHIS, using the current insurance coverage as a proxy for this estimation (42). The 62% who are uninsured either pay out of pocket to access tamoxifen or do not get tamoxifen if they are unable to afford it. The proportions of women likely to present with early or advanced breast cancer was also derived from the findings of Ohene-Yeboah and Adjei (205) who confirmed the stage of breast cancer through histopathology grading.

9.2.3 Summary of input data and their sources

Table 9-1 presents a summary of the data used for the BIA and their sources. Resource use was estimated with input from a Ghanaian clinical expert as reported in the economic evaluations (Chapters 7 and 8). The unit costs of tamoxifen and associated costs such as the costs of follow-up medications and treatments were derived from the NHIS medicines list and the NHIS tariffs for tertiary hospitals. The current market price of tamoxifen that was used in a sensitivity analysis was derived with input from the clinical expert.

Table 9-1: Summary of input parameters and their data sources

Parameter	Value	Source
Proportion of women insured under the NHIS	38%	MOH 2015
Proportion of women likely to experience adverse events	24%	Ghanaian clinical expert
Population of pre and peri-menopausal women at risk	7,657,155	Ghana statistical service Wiredu and Armah 2006
Prevalence of breast cancer	58 per 100,000	KATH administrative data on breast cancer
Percentage of hormone receptor positive women	60%	Ohene-Yeboah and Adjei 2012
Proportions of women with advanced and early breast cancer	85% advanced breast cancer 15% early breast cancer	Ohene-Yeboah and Adjei 2012
Resource use	Not applicable	Ghanaian clinical expert
Cost of tamoxifen – NHIS reimbursement price	GHC 1.2 (AUD 0.35) per tablet	NHIS medicines list 2017
Cost of tamoxifen – current market value	GHC 2.00 (AUD 0.58) per tablet	KATH medicines list
Cost of calcium tablets	GHC 0.5 (AUD 0.15) per tablet	NHIS medicines list 2017
Cost of follow-up visits	GHC 26.04 (AUD 7.55)	NHIS tariffs for tertiary hospitals
Frequency of follow-up visits	Twice in a year for advanced breast cancer Four times in a year for early breast cancer	Ghanaian clinical expert
Cost of treating initial adverse effects due to tamoxifen	GHC 315.22 (AUD 91.41)	NHIS medicines list 2016/2017

Note: AUD: Australian dollars, GHC: Ghana cedis. 1 GHC is equivalent to AUD 0.29.

9.2.4 Analytical approach

Estimation of use and costs of tamoxifen

Table 9-2 presents all the assumptions used in this analysis. One major assumption underpinning this analysis is that women who are likely to report to the hospital for treatment of breast cancer are those currently insured under the NHIS. Therefore, to estimate this value, the reported proportion of the Ghanaian population currently enrolled under the NHIS was used as shown in Figure 9-1. This assumption was validated using the number of women who were receiving tamoxifen under the NHIS as at the end of year 2017 at the KATH (360 women). Therefore, if a similar number is assumed for Korle Bu Teaching Hospital that has an oncology centre, it is estimated that a total of 720 women are seen in a year. This number is close to the

1016 patients estimated to receive tamoxifen in year 1 (2018, for this study), taking into account patients who might have died before the year ended.

Table 9-2: List of assumptions underpinning the BIA

Number	Assumptions	Source
1.	Women who are not insured under the NHIS are not likely to seek care at the hospital, hence do not have access to tamoxifen	MOH 2015
2.	The proportion of women taking tamoxifen who are currently insured under the NHIS is 38%	MOH 2015
3.	The prevalence rate of breast cancer over the five-year period is constant	Ghanaian clinical expert
4.	Pre- and peri-menopausal women are those between the ages of 15 years and 50 years	Ghana Statistical Service Wiredu and Armah 2006
5.	Adverse events likely to be experienced by patients taking tamoxifen are vaginal bleeding, musculoskeletal disorders (arthritis, arthralgia, myalgia), deep vein thrombosis and pulmonary embolism	EBCTCG 2011, Ghanaian clinical expert
6.	Of the adverse events, vaginal bleeding, deep vein thrombosis and pulmonary embolism are assumed to occur once; therefore, the cost of treatment is incurred once in during the period when a patient takes tamoxifen. Musculoskeletal disorders are assumed to occur throughout the period of tamoxifen intake. Hence, calcium tablets are given together with tamoxifen to patients who experience these	Ghanaian clinical expert
7.	10% of women will experience vaginal bleeding, 24% musculoskeletal disorders, 1% pulmonary embolism and 1% deep vein thrombosis as adverse events due to tamoxifen	Ghanaian clinical expert
8.	The stage of breast cancer of a patient does not affect her probability of experiencing an adverse event; neither does it affect the severity of the adverse event. Therefore, every patient has the same probability of experiencing an adverse event, hence, would require the same resources to treat it	EBCTCG 2011, Ghanaian clinical expert

The current national strategy for breast cancer control (designed in 2011) suggested measures such as educating young girls and women so they conduct breast self-examination, have a clinical breast examination every three years (for women below 35 years) and have a mammography (for women who are 40 years and above) to increase early detection of breast cancer (289). In spite of these recommendations, no policy has been enacted to implement them; hence this analysis assumed a constant prevalence rate for the five-year time horizon under the assumption that there are no policies that could be anticipated to change the prevalence rate in the next five years.

The same proportion of patients assumed to experience adverse events during tamoxifen treatment in the economic evaluations conducted in Chapters 7 and 8 were utilised in the BIA as described in Table 9-2. Adverse events assumed to be experienced once are categorised as initial adverse events, and their costs are incurred once. Musculoskeletal disorders (an ongoing adverse event) which were assumed to occur throughout the period of tamoxifen therapy are treated with calcium tablets that are administered together with tamoxifen, hence these costs are borne by the NHIS. It was further assumed that the number and intensity of adverse events experienced by women on tamoxifen was not dependent on the stage of breast cancer (213) (with inputs from clinical expert). As such, every woman (either with early or advanced breast cancer) had the same probability of experiencing an adverse event and utilised the same resources in their treatment.

As reported in the economic evaluations in Chapters 7 and 8, the additional benefit of tamoxifen was due to the quality of life of patients and not simply the duration of life. Hence, it was assumed that patients on tamoxifen would have a better quality of life with little or no pain depending on the stage of cancer. The costs of analgesics were assumed to be similar for patients on tamoxifen and patients not receiving tamoxifen, even though tamoxifen is expected to reduce the incidence of pain associated with cancer recurrence. As the side effects of tamoxifen include tumour pain and flaring, patients on tamoxifen still experience pain. Therefore, in Ghanaian clinical practice, patients are given analgesics irrespective of receiving or not receiving tamoxifen. In addition, studies used as source of clinical efficacy data (both RCTs and cohort studies did not report treatment of pain due to breast cancer in both treatment arms. Hence, the cost of analgesics used in the treatment of pain was excluded from the analysis.

Additional costs due to tamoxifen included in the analysis are the costs of follow-up visits to refill drug prescriptions. As reported earlier on in this thesis, patients with early breast cancer

make four follow-up visits in a year and those with advanced breast cancer make two follow-up visits in a year (Ghanaian clinical expert), each costing GHC 26.04 (AUD 7.55).

As mentioned in Chapter 6, section 6.2.1, the current market price of tamoxifen is higher than the current reimbursement price listed by the NHIS: GHC 2.00 (AUD 0.58); GHC 1.2 (AUD 0.35) per tablet (Ghanaian clinical expert). Consequently, women incur out of pocket expenses to make up for the difference in prices as co-payments in accessing tamoxifen. A major driver of this difference was attributed to the instability of the foreign exchange rate of the Ghana cedi. Table 9-3 presents the foreign exchange rates of the Ghana cedi against the USD and AUD from 2015, when the market survey was conducted for the prices of medicines used to inform the NHIS medicines reimbursement price list, to the end of 2017. By the end of 2017, the GHC had depreciated by GHC 1.18 (37%). It is worth noting that prices of goods did not decrease in periods of GHC appreciation compared to previous months (217, 219).

Table 9-3: Trend in the foreign exchange rates between the GHC and other currencies (USD and AUD) from 2015 to end of 2017

Year	GHC equivalence to 1 USD	GHC equivalence to 1 AUD
2015		
January	3.23	2.61
April	3.80	2.95
August	4.31	2.91
December	3.79	2.74
2016		
January	3.82	2.69
April	3.83	2.93
August	3.95	3.02
December	4.15	2.98
2017		
January	4.24	3.22
April	4.17	3.15
August	4.39	3.47
December	4.41	3.41

Source: http://www.bog.gov.gh/markets/daily-interbank-fx-rates
NB: Selling rates are reported.

Another reason for this observed difference can be attributed to the fact that the NHIS has not reviewed the prices of their services and listed drugs for the past two years. Therefore, to

account for the difference between the price of tamoxifen reimbursed by the NHIS and what patients pay, the co-payments made by patients are estimated in the base case analysis. A sensitivity analysis examines a scenario in which the NHIS pays the full cost of tamoxifen.

The financial impact of tamoxifen to the NHIS was estimated for each year over the five-year time horizon of the analysis. The cost of tamoxifen to the NHIS per year was calculated as the sum of the annual cost of tamoxifen, the annual cost of initial adverse events, the annual cost of calcium tablets (for ongoing adverse events) and the annual cost of follow-up visits per year. The annual cost of each cost item for the target population was estimated as the product of price per unit, frequency of use per year and number of target population.

Estimation of changes in use and cost of other drugs

As discussed in Chapter 6 section 6.2.2, the best comparator for tamoxifen was no tamoxifen. Therefore, for the purposes of the BIA to the NHIS, tamoxifen was assumed to substitute for care provided in instances where patients do not receive tamoxifen due to their inability to afford it. Routine care for patients who do not receive tamoxifen under the NHIS was assumed similar to that given for HR negative patients. The focus of treatment for these patients is management of pain. Hence, the costs expected to be substituted by tamoxifen will be that of analgesics.

Nonetheless, as discussed above, the difference in cost of analgesics used by patients not receiving tamoxifen and those on tamoxifen is assumed to be similar. As a result, the cost of substituted treatment is omitted from the analysis.

9.2.5 Sensitivity analysis

Univariate sensitivity analysis

One-way sensitivity analysis was conducted on parameters that were deemed uncertain and those assumed to change over time to show the impact of varying these variables on the base case results. The variables varied were the cost of tamoxifen, calcium tablets and follow-up visits. In the base case, cost of tamoxifen, calcium tablets and follow-up visits were assumed to be stable over the five-year period. However, due to fluctuations in the foreign exchange rate of the GHC, instability in the market price of goods and services in Ghana is assumed. Therefore, variations were done by increasing or decreasing the costs by selected percentages to reflect these changes. Table 9-4 presents the ranges used in the univariate sensitivity analysis.

Table 9-4: Parameter ranges used for the univariate analysis – BIA

Parameter	Base estimate	Percentage varied	Range for sensitivity analysis (GHC)	
			Lower bound	Upper bound
Cost of tamoxifen	1.20			
		20%	0.96	1.44
		40%	0.72	1.68
		50%	0.60	1.80
		70%	0.36	2.04
		80%	0.24	2.16
		100%	0.00	2.40
Cost of follow-up visits	26.04			
		10%	23.44	28.64
		20%	20.83	31.25
		30%	18.23	33.85
		50%	13.02	39.06
		60%	10.42	41.66
		100%	0.00	52.08
Cost of calcium tablets	0.50			
		10%	0.45	0.55
		20%	0.40	0.60
		30%	0.35	0.65
		50%	0.60	0.75

Scenario analysis: Using the GLOBOCAN prevalence rate

The prevalence rate of breast cancer in Ghana as estimated by GLOBOCAN was used to examine its impact on the net cost of tamoxifen to the NHIS. Unlike the base case, the prevalence rate of breast cancer varied over the years. All other assumptions used for the base case were maintained.

Scenario analysis: Variation in NHIS coverage

In the pursuit of universal health coverage, it is expected that the NHIS coverage would increase over time. To account for the potential increase in the population covered by the NHIS, this scenario includes the expected increase in the NHIS budget with concomitant increase in the number of people who are insured. The coverage was varied upward by 10% until full coverage was reached: 50%, 60%, 70%, 80%, 90% and 100%.

Scenario analysis: Variation in NHIS coverage and price of tamoxifen

This scenario was carried out under the assumption that the NHIS will reimburse tamoxifen for its current market price, and the NHIS coverage would vary over time. As indicated in the previous chapters, the current market price of tamoxifen is higher than the current NHIS reimbursement price. Thus, change in insurance coverage was varied simultaneously with the change in the price of tamoxifen, that is, the market price.

Scenario analysis: Change in the proportions of stages of breast cancer diagnosis

The proportions of advanced and early breast cancer were varied using estimates reported for South African and Moroccan women (290, 291), which were lower that the advanced breast cancer estimate for Ghana. These values were used under the assumption that should breast cancer screening increase in Ghana, more breast cancer cases will be detected in the early stages compared to the current situation. The proportions used in the sensitivity analysis for early

breast cancer versus advanced breast cancer were 50% versus 50%, 67% versus 33% and 80% versus 20%.

Scenario analysis: Inclusion of costs due to productivity loss in caregiving

Chapter 8 demonstrated that, for advanced breast cancer, patients and families incur costs that were 63% higher than health system costs. Most of these costs were associated with lost productivity due to care giving, in the absence of palliative care services in the Ghanaian health system. This scenario therefore estimates the total cost of tamoxifen should these productivity loss costs be replaced by palliative care costs borne by the NHIS.

9.3 Results

9.3.1 Base case results

The number of women projected to have breast cancer in the first year, 2018, was 4,456, 60% (n=2,673) of whose cancers were predicted to be HR positive. Of the HR positive breast cancer patients, 38% (n=1,016) are expected to be insured under the NHIS, and 85% will present with advanced stage breast cancer at diagnosis. In year five, 2022, the prevalence of HR positive breast cancer among pre- and peri-menopausal Ghanaian women was projected to be 2,912. Table 9-5 presents the number of pre and peri-menopausal women predicted to have HR positive breast cancer over the five-year period, and as such be prescribed tamoxifen.

Table 9-5: Number of pre and peri-menopausal women predicted to use tamoxifen

Description	Year 1	Year 2	Year 3	Year 4	Year 5
Number of pre- and peri-menopausal women (aged 15-49)	7,657,155	7,824,081	7,992,299	8,164,134	8,339,663
Number of women likely to get breast cancer	4,456	4,553	4,651	4,751	4,853
Number of women with hormone receptor positive breast cancer	2,673	2,732	2,790	2,850	2,912
Number of women insured under the NHIS	1,016	1,038	1,060	1,083	1,106
Number of women with advanced breast cancer	864	882	901	921	940
Number of women with early breast cancer	152	156	159	162	166

Table 9-6 presents the cost of tamoxifen usage per woman per year. The cost of tamoxifen per woman per year was calculated as GHC 438 (AUD 127) for both advanced and early breast cancer. However, the total annual NHIS cost of tamoxifen for a woman who also experiences musculoskeletal symptoms was estimated as GHC 673 (AUD 195) for advanced breast cancer and GHC 725 (AUD 210) for early breast cancer.

Table 9-6: Cost of tamoxifen usage per woman per year

Description	Unit cost (GHC (AUD))	Frequency of usage	Total cost per year (GHC (AUD))
Advanced breast cancer			
Cost of tamoxifen to the NHIS	1.20 (0.35)	365	438.00 (127.02)
Cost of tamoxifen to the patient (co-payment)	0.8 (0.23)	365	292 (84.68)
Cost of follow-up visits	26.04 (7.55)	2	52.08 (15.10)
Cost of calcium tablets	0.50 (0.15)	365	182.50 (52.93)
Cost of other adverse events	315.22 (91.41)	1	315.22 (91.41)
Total cost per year			***987.80 (287.46)***
Early breast cancer			
Cost of tamoxifen	1.20 (0.35)	365	438.00 (127.02)
Cost of tamoxifen to the patient (co-payment)	0.8 (0.23)	365	292 (84.68)
Cost of follow-up visits	26.04 (7.55)	4	104.16 (30.21)
Cost of calcium tablets	0.50 (0.15)	365	182.50 (52.93)
Cost of other adverse events	315.22 (91.41)	1	315.22 (91.41)
Total cost per year			***1,039.88 (301.56)***

Note: Costs are presented in GHC (AUD). AUD: Australian dollars, GHC: Ghana cedis. 1 GHC is equivalent to AUD 0.29.

Table 9-7 presents the net cost of tamoxifen per stage of breast cancer to the NHIS for the first five years after diagnosis. In year one, the net cost of tamoxifen was estimated at GHC 526,325 (AUD 152,634) for advanced breast cancer and GHC 100,817 (AUD 29,237) for early breast cancer. In same year, patients will incur GHC 252,139 (AUD 73,120) out of pockets costs under the current payment arrangements for tamoxifen. With increases in the prevalence of breast cancer each year, the net cost of tamoxifen usage is expected to increase by 9% in the 5th year for both advanced and early breast cancer: GHC 573,238 (AUD 166,239) and GHC 109,803 (AUD 31,843) respectively.

Table 9-7: Net cost of tamoxifen usage according to stage of breast cancer

Description	Year 1 (GHC (AUD))	Year 2 (GHC (AUD))	Year 3 (GHC (AUD))	Year 4 (GHC (AUD))	Year 5 (GHC (AUD))
Advanced breast cancer					
Number of pre- and peri-menopausal women given tamoxifen under the NHIS	863	882	901	921	940
Cost of tamoxifen per woman to the NHIS	438 (127)	438 (127)	438 (127)	438 (127)	438 (127)
Cost of tamoxifen per woman to the patient (co-payment)	292 (85)	292 (85)	292 (85)	292 (85)	292 (85)
Total cost of tamoxifen to the NHIS	378,208 (109,680)	386,453 (112,071)	394,762 (114,481)	403,249 (116,942)	411,919 (119,457)
Total cost of tamoxifen to the patient (co-payment)	252,139 (73,120)	257,635 (74,714)	263,175 (76,321)	268,833 (77,962)	274,613 (79,638)
Cost of follow-up visits	52 (15)	52 (15)	52 (15)	52 (15)	52 (15)
Total costs of follow-up visits	44,971 (13,042)	45,951 (13,326)	46,939 (13,612)	47,948 (13,904)	48,979 (14,204)
Proportions of women likely to have adverse events	207	212	216	221	226
Cost of calcium tablets	183 (53)	183 (53)	183 (53)	183 (53)	183 (53)
Cost of initial adverse events	315 (91)	315 (91)	315 (91)	315 (91)	315 (91)
Total cost of calcium tablets	37,821 (10,968)	38,645 (11,207)	39,477 (11,448)	40,325 (11,694)	41,192 (11,946)
Total cost of initial adverse events	65,325 (18,944)	66,750 (19,357)	68,185 (19,774)	69,651 (20,199)	71,148 (20,633)
Net cost of tamoxifen due to advanced breast cancer to the NHIS	526,325 (152,634)	537,799 (155,962)	549,361 (159,315)	561,173 (162,740)	573,238 (166,239)
Net cost of tamoxifen due to advanced breast cancer	*778,464* (225,755)	*795,434* (230,676)	*812,536* (235,636)	*830,006* (240,702)	*847,851* (245,877)
Early breast cancer					
Number of pre- and peri-menopausal women managed with tamoxifen	152	156	159	162	166
Cost of tamoxifen per woman to the NHIS	438 (127)	438 (127)	438 (127)	438 (127)	438 (127)
Cost of tamoxifen per woman to the patient (co-payment)	292 (85)	292 (85)	292 (85)	292 (85)	292 (85)
Total cost of tamoxifen to the NHIS	66,743 (19,355)	68,198 (19,777)	69,664 (20,203)	71,162 (20,637)	72,692 (21,081)
Total cost of tamoxifen to the patient (co-payment)	44,495 (12,904)	45,465 (13,185)	46,443 (13,468)	47,441 (13,758)	48,461 (14,054)
Cost of follow-up visits	104 (30)	104 (30)	104 (30)	104 (30)	104 (30)
Total costs of follow-up visits	15,872 (4,603)	16,218 (4,703)	16,567 (4,804)	16,923 (4,908)	17,287 (5,013)

Description	Year 1 (GHC (AUD))	Year 2 (GHC (AUD))	Year 3 (GHC (AUD))	Year 4 (GHC (AUD))	Year 5 (GHC (AUD))
Proportions of women likely to experience adverse events	37	37	38	39	40
Cost of calcium tablets	183 (53)	183 (53)	183 (53)	183 (53)	183 (53)
Cost of initial adverse events	315 (91)	315 (91)	315 (91)	315 (91)	315 (91)
Total cost of calcium tablets	6,674 (1,936)	6,820 (1,978)	6,967 (2,020)	7,116 (2,064)	7,269 (2,108)
Total cost of initial adverse events	11,528 (3,343)	11,779 (3,416)	12,033 (3,490)	12,291 (3,565)	12,556 (3,641)
Net cost of tamoxifen due to early breast cancer to the NHIS	100,817 (29,237)	103,015 (29,874)	105,230 (30,517)	107,492 (31,173)	109,803 (31,843)
Net cost of tamoxifen due to early breast cancer	*145,312* (42,141)	*148,480* (43,059)	*151,673* (43,985)	*154,933* (44,931)	*158,264* (45,897)

Note: Costs are presented in GHC (AUD). AUD: Australian dollars, GHC: Ghana cedis. 1 GHC is equivalent to AUD 0.29.

Table 9-8 presents the net total cost of tamoxifen to the NHIS according to the individual cost items. For example, the net cost of tamoxifen to the NHIS for year one was estimated as GHC 627,142 (AUD 181,871). As expected, the acquisition cost of tamoxifen constituted the highest proportion (71%) of the net cost. The cost of treating initial adverse events was the next highest cost item, accounting for 12% of the net cost to the NHIS, followed by costs of follow-up visits (11%).

Table 9-8: Net total cost of tamoxifen for breast cancer

Description	Year 1 (GHC (AUD))	Year 2 (GHC (AUD))	Year 3 (GHC (AUD))	Year 4 (GHC (AUD))	Year 5 (GHC (AUD))
Total cost of tamoxifen to the NHIS	444,951 (129,036)	454,651 (131,849)	464,426 (134,683)	474,411 (137,579)	484,611 (140,537)
Total cost of tamoxifen to the patient (co-payment)	296,634 (86,024)	303,101 (87,899)	309,617 (89,789)	316,274 (91,719)	323,074 (93,691)
Total cost of tamoxifen	741,585 (215,060)	757,751 (219,748)	774,043 (224,472)	790,685 (229,299)	807,685 (234,229)
Total cost of follow-up visits	60,843 (17,644)	62,169 (18,029)	63,506 (18,417)	64,871 (18,813)	66,266 (19,217)
Total cost of calcium tablets	44,495 (12,904)	45,465 (13,185)	46,443 (13,468)	47,441 (13,758)	48,461 (14,054)
Total cost of initial adverse events	76,853 (22,288)	78,529 (22,773)	80,217 (23,263)	81,942 (23,763)	83,704 (24,274)
Net total cost of tamoxifen to the NHIS	***627,142 (181,871)***	***640,813 (185,836)***	***654,591 (189,831)***	***668,665 (193,913)***	***683,041 (198,082)***
Net total cost of tamoxifen	***923,776 (267,895)***	***943,914 (273,735)***	***964,208 (279,620)***	***984,939 (285,632)***	**1,006,115 (291,773)**

Note: Costs are presented in GHC (AUD). AUD: Australian dollars, GHC: Ghana cedis. 1 GHC is equivalent to AUD 0.29.

9.3.2 Sensitivity analysis

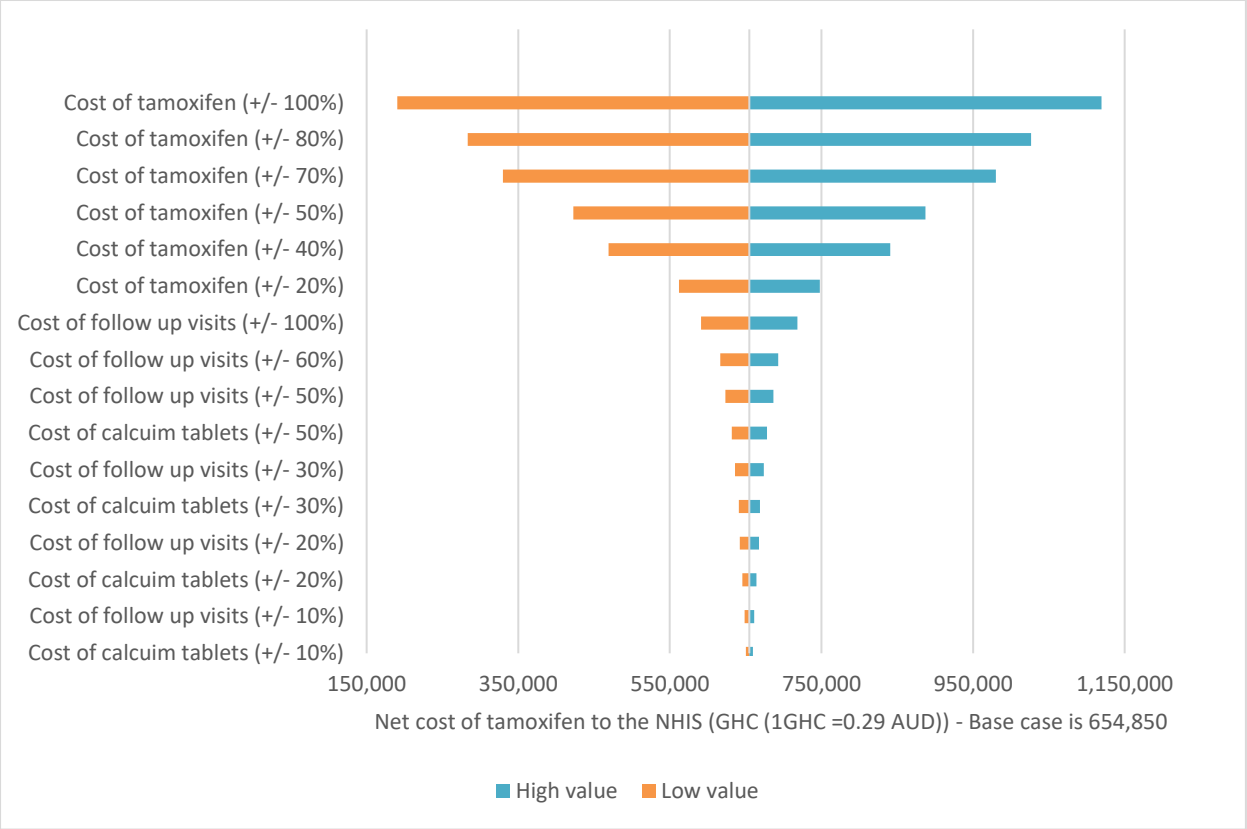
Univariate sensitivity analysis

Figure 9-2 presents the results of univariate sensitivity analysis. A 50% increase in the cost of tamoxifen led to a 36% increment in the net cost of tamoxifen to the NHIS (GHC 887,155 (AUD 257,275)) and vice versa. Similarly, a 100% increase led to a 71% rise in the net cost of tamoxifen and vice versa.

When the cost of calcium is decreased or increased under similar assumptions, the net total cost of tamoxifen to the NHIS will decrease or increase but by a lower margin compared to the acquisition cost of tamoxifen. For example, a 50% rise in the cost of calcium tablets will result in a 4% increase in the base case results (GHC 678,081 (AUD 196,643)) and vice versa.

As shown in Figure 9-2, a 50% or 100% increment in costs of follow-up visits will lead to a 4.8% or 9.7% increase in costs of the base case respectively, and vice versa. Appendix 7, Table

11-13 presents the yearly net costs of tamoxifen to the NHIS for each parameter presented in the tornado diagram in Figure 9-2.



Note: All costs are presented in GHC (1 GHC=AUD 0.29). Costs presented are the average annual net cost.

Figure 9-2: Tornado diagram presenting the results of a univariate sensitivity analysis of selected study parameters

Scenario analysis: Using the GLOBOCAN prevalence rate

Table 9-9 presents the number of pre- and peri-menopausal women predicted to use tamoxifen when the GLOBOCAN prevalence estimate was used. The number of patients predicted to be HR positive was higher than that used in the base case. For example, in the first year, compared to the base case, 49% more patients were predicted to be HR positive (n=5,205).

Table 9-9: Number of pre- and peri-menopausal women predicted to use tamoxifen – GLOBOCAN prevalence estimate

Description	Year 1	Year 2	Year 3	Year 4	Year 5
Number of pre- and peri-menopausal women (aged 15-49)	7,657,155	7,824,081	7,992,299	8,164,134	8,339,663
Number of women likely to get breast cancer	8,675	10,204	11,792	13,444	15,161
Number of women with hormone receptor positive breast cancer	5,205	6,123	7,075	8,066	9,097
Number of women insured under the NHIS	1,978	2,327	2,689	3,065	3,457
Number of women with advanced breast cancer	1,681	1,978	2,285	2,605	2,938
Number of women with early breast cancer	297	349	403	460	519

Table 9-10 further presents the net cost of using tamoxifen to the NHIS using the GLOBOCAN prevalence rate. The predicted net cost for year one was GHC 1,221,094 (AUD 354,117), which is 49% higher than the base case results. The net cost for the remaining years compared to the base case estimates were all higher.

Table 9-10: Results of selected univariate sensitivity analysis of base case net cost of tamoxifen to the NHIS

Description	Year 1 (GHC (AUD))	Year 2 (GHC (AUD))	Year 3 (GHC (AUD))	Year 4 (GHC (AUD))	Year 5 (GHC (AUD))
WHO GLOBOCAN prevalence estimate					
Total cost of tamoxifen for advanced breast cancer	1,024,796 (297,191)	1,205,405 (349,568)	1,392,993 (403,968)	1,588,090 (460,546)	1,790,932 (519,370)
Total cost of tamoxifen for early breast cancer	196,298 (56,927)	230,894 (66,959)	266,826 (77,380)	304,197 (88,217)	343,051 (99,485)
Net cost of tamoxifen for breast cancer to the NHIS	1,221,094 (354,117)	1,436,299 (416,528)	1,659,819 (481,348)	1,892,287 (548,763)	2,133,983 (618,855)
Base case weighted by the average WHO GLOBOCAN prevalence estimate					
Total cost of tamoxifen for advanced breast cancer	1,334,580 (387,028)	1,363,674 (395,466)	1,392,993 (403,968)	1,422,943 (412,653)	1,453,536 (421,525)
Total cost of tamoxifen for early breast cancer	255,637 (74,135)	261,210 (75,751)	266,826 (77,380)	272,563 (79,043)	278,423 (80,743)
Net cost of tamoxifen for breast cancer to the NHIS	1,590,218 (461,163)	1,624,884 (471,216)	1,659,819 (481,348)	1,695,505 (491,697)	1,731,959 (502,268)
Current market price of tamoxifen					
Total cost of tamoxifen for advanced breast cancer	779,724 (226,120)	796,722 (231,050)	813,852 (236,017)	831,350 (241,091)	849,224 (246,275)
Total cost of tamoxifen for early breast cancer	145,534 (42,205)	148,707 (43,125)	151,904 (44,052)	155,170 (44,999)	158,506 (45,967)
Net cost of tamoxifen for breast cancer to the NHIS	925,259 (268,325)	945,429 (274,175)	965,756 (280,069)	986,520 (286,091)	1,007,730 (292,242)

Note: Costs are presented in GHC (AUD). AUD: Australian dollars, GHC: Ghana cedis..1 GHC is equivalent to AUD 0.29.

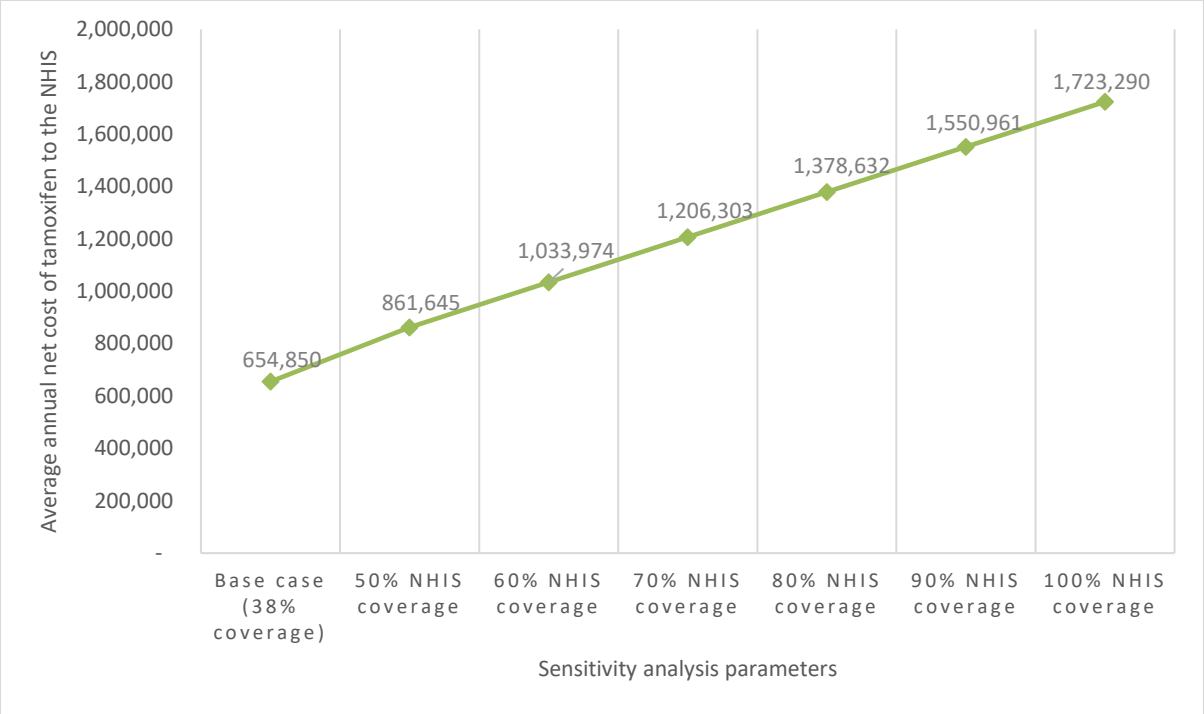
The prevalence rate of breast cancer used in the base case was varied to reflect possible changes in the prevalence rate over time. The prevalence rate was increased by 0.00148 (that is, 148 per 100, 000 women) per year, using the average annual increase in the prevalence of breast cancer reported by GLOBOCAN. The net total cost to the NHIS was GHC 1,590,218 (AUD 461,163) for the first year, which is expected to increase to GHC 1,731,959 (AUD 502,268) by year five (Table 9-10).

Using the current market price of tamoxifen for the BIA, it would cost the NHIS more to reimburse 100% of the tamoxifen price (Table 9-10). For example, in year one, the NHIS would need an additional GHC 298,111 (AUD 86,452) to fully reimburse tamoxifen for the treatment of breast cancer compared with the current rate of NHIS coverage.

Scenario analysis – Variation in NHIS coverage

Figure 9-3 presents the results of a scenario analysis when the NHIS insurance coverage rate is varied. In this figure, the costs are presented as the average annual net cost of tamoxifen to the NHIS for easy description (see Appendix 7, Table 11-13 for a detailed description of the net cost of tamoxifen per year for this scenario analysis). An increase in NHIS coverage meant an increase in the proportion of women who will be covered under the NHIS and are likely to receive tamoxifen for the treatment of breast cancer under the NHIS, and subsequently, an increase in costs to the NHIS. However, costs will be saved from the societal perspective through increase in productivity and a removal of out of pocket costs incurred by women and their family for breast cancer treatment. For instance, 60% insurance coverage results in an average annual net cost of GHC 1,033,974 (AUD 299,853) for tamoxifen to the NHIS, a 37% increase in the average net cost of tamoxifen over the base case. Similarly, the NHIS would require additional funds to reimburse tamoxifen if insurance coverage is to increase above base

case, with more than an estimated 100% increment in the current budget when insurance coverage increases beyond 70%.

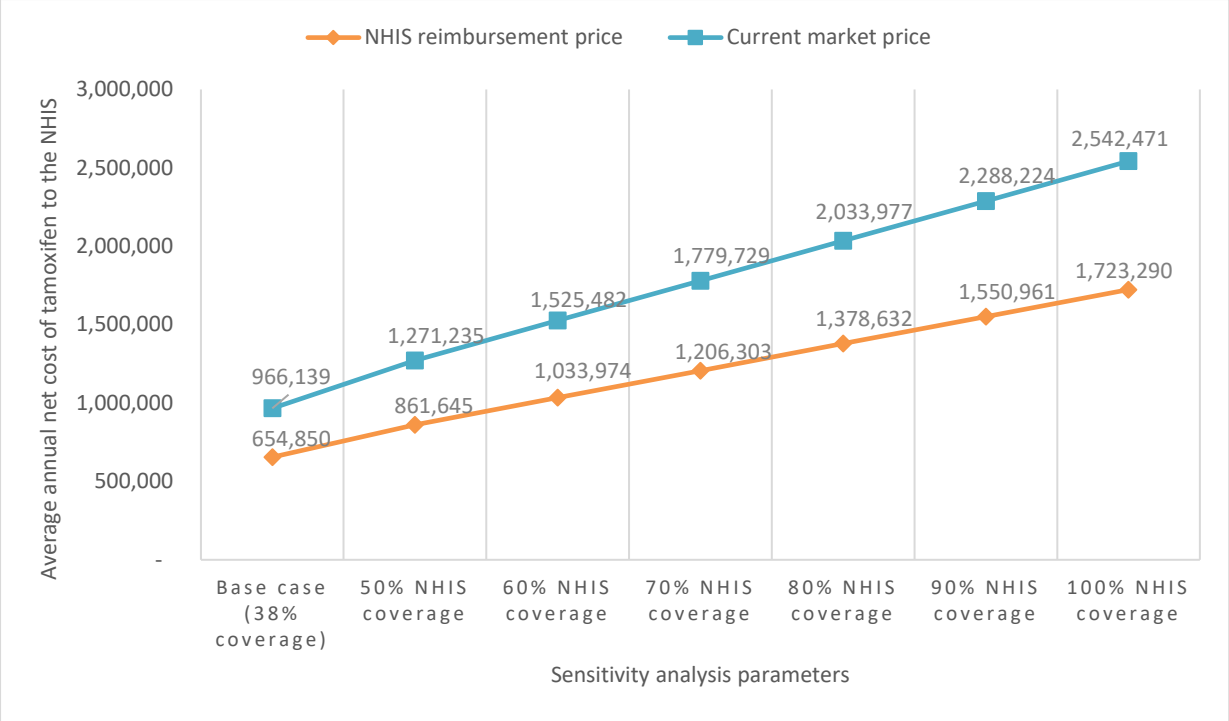


Note: All costs are presented in GHC (1GHC=AUD 0.29). Costs presented are the average annual net cost.

Figure 9-3: Average annual net cost of tamoxifen to the NHIS when insurance coverage was varied

Scenario analysis – variation in both NHIS coverage and price of tamoxifen

Furthermore, using the current market price of tamoxifen for the analysis implies the NHIS would need to allocate more funds to reimburse tamoxifen. For example, assuming 50% NHIS coverage and 100% reimbursement of the current market price of tamoxifen leads to a 95% increase in the base case (GHC 1,271,235 (AUD 368,658). When compared with the same NHIS coverage rate but assuming the current reimbursement price of tamoxifen, the former is 48% higher than the latter. Figure 9-4 presents a comparison of variation of NHIS coverage for the current NHIS reimbursement price and market price of tamoxifen.



Note: All costs are presented in GHC (1 GHC=AUD 0.29). Costs presented are the average annual net cost.

Figure 9-4: Comparison of current NHIS reimbursement price with the market price for tamoxifen when insurance coverage is varied

Scenario analysis - Variation in proportions of stages of breast cancer diagnosis

Figure 9-5 presents the results of a scenario analysis when the proportions of advanced and early breast cancer cases are varied. To get a better picture of what the NHIS is likely to spend when the current price at which tamoxifen is reimbursed is reviewed to reflect the current market price, this scenario analysis compares the annual average net cost of tamoxifen to the NHIS for the base case and the current market price of tamoxifen.

A 65% increase in early breast cancer cases, for example through an early breast cancer screening program, (so that 80% are early stage and 20% are advanced) will lead to an increase in the annual average net cost of tamoxifen compared to the base case: GHC 690,759 (AUD 200,320) versus GHC 654,850 (AUD 189,907). Appendix 7, Table 11-13 presents detailed results for the net cost of tamoxifen per year for this scenario analysis. The increase in net total

cost to the NHIS is due to an increase in the number of follow-up visits for patients with early breast cancer. If the proportions of women with advanced breast cancer falls to 33% or 50% relative to those with early breast cancer, costs to the NHIS will also increase (Figure 9-5).

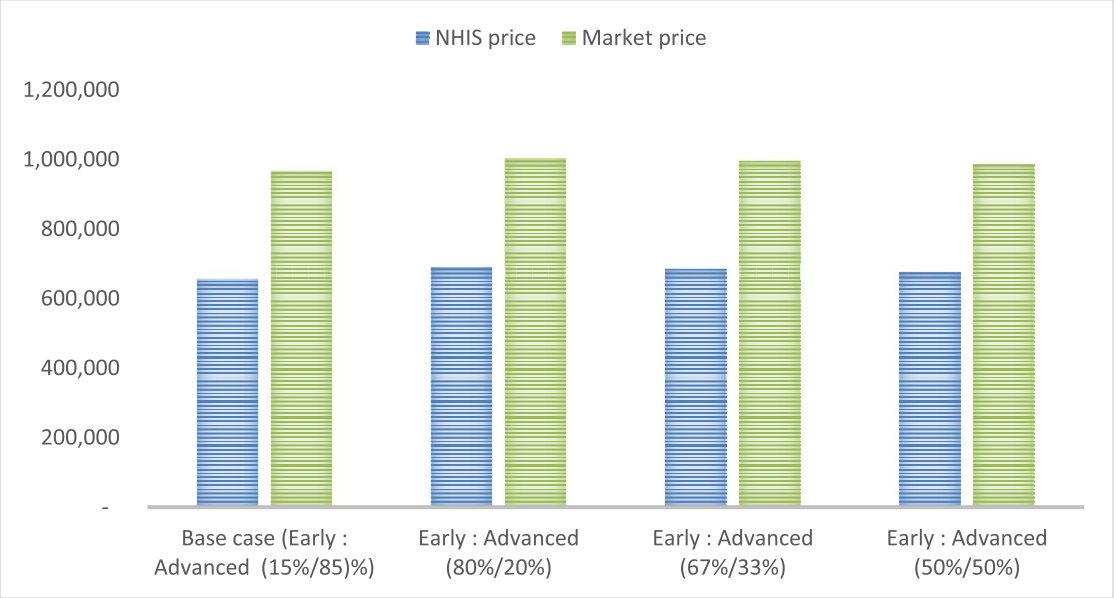


Figure 9-5: Average annual net cost of tamoxifen to the NHIS when proportions of breast cancer stage on diagnosis is varied

Scenario analysis: Inclusion of costs due to productivity loss in caregiving

Including the costs due to lost productivity in caregiving increased the net cost of tamoxifen by more than 200%. This implies that lost productivity of family caregivers, assumed as synonymous with the costs of palliative care services, constitutes a higher proportion of costs.

Table 9-11: Net cost of tamoxifen when costs due productivity loss associated with caregiving is included

Description	Year 1 (GHC (AUD))	Year 2 (GHC (AUD))	Year 3 (GHC (AUD))	Year 4 (GHC (AUD))	Year 5 (GHC (AUD))
Early breast cancer	145,312 (42,140)	148,480 (43,059)	151,672 (43,985)	154,933 (44,931)	158,264 (45,897)
Advanced breast cancer	2,829,129 (820,447)	2,890,804 (838,333)	2,952,957 (856,357)	3,016,445 (874,769)	3,081,299 (893,577)
Net cost of tamoxifen	2,974,441 (862,588)	3,039,284 (881,392)	3,104,629 (900,342)	3,171,378 (919,700)	3,239,563 (939,473)

Note: Costs are presented in GHC (AUD). AUD: Australian dollars, GHC: Ghana cedis. 1 GHC is equivalent to AUD 0.29.

9.4 Discussion

At the current price and 38% insurance coverage, the NHIS would require an average of GHC 654,850 (AUD 189,907) per year to fund tamoxifen for the treatment of both early and advanced breast cancer. This constitutes 0.08% of the total claims expenditure of the NHIS (50). Of this amount, 29% is attributed to costs other than the acquisition price of tamoxifen (such as cost of follow-up visits and treating adverse events due to tamoxifen intake). Changes in the NHIS coverage (upwards) would mean an increase in the cost of tamoxifen treatment as a percentage of the total NHIS claims expenditure. Hence, to be able to do this, additional resources will be required to fund tamoxifen, which will mean displacing some services should the NHIS budget remain the same. The cost of adverse events and follow-up visits had a minimal impact on the net cost of tamoxifen.

This estimated net cost of tamoxifen to the NHIS does not represent the true cost of tamoxifen as patients are required to spend out of pocket as co-payment for the drug because of a 40% difference between the current market price and the NHIS reimbursement price of tamoxifen. However, under the NHIA Act 852 (220), the NHIS is supposed to reimburse the full cost of any health technology listed under the benefit scheme. Therefore, should the current reimbursement price be revised to reflect the current market price of tamoxifen as done annually and in accordance with the NHIA Act 625, the NHIS would require an additional GHC 311,289 (AUD 90,274) per year on average to fill the gap in the current funding arrangement, if all patients are compliant. In the case that insured patients default from tamoxifen treatment, the estimated financial impact of tamoxifen on the NHIS is expected to reduce by the proportion of patients that become noncompliant and stop receiving tamoxifen treatment. On the other hand, the reduction in the financial impact of tamoxifen on the NHIS due to insured patients defaulting may shift the costs to other part of the NHIS (due to increase

in medical costs incurred from treating symptoms of progression) and the patient and family as well. The net cost of tamoxifen is sensitive to changes in the price of tamoxifen.

Fluctuations in the foreign exchange rates is a key contributory factor to the difference in NHIS reimbursement price and the market value of tamoxifen, and consequently 'informal' co-payment arrangements. A number of studies and government report have reported the negative impact of the instability of the foreign exchange rate (especially the GHC depreciation against the USD) on consumer prices, inflation rates and inter-bank interest rates (216-219, 292, 293). Subsequently, the impact of foreign exchange rates on the prices of goods is observed in sectors of Ghana's economy that are dependent on imported goods. Such goods include machinery, petroleum products and some agricultural goods. Thus, in conducting BIA, it is important to consider the impact of fluctuations of foreign exchange rates on prices of health technologies either in the base case or in a sensitivity analysis as demonstrated in this study. This is because for example, in the year 2015, 1 USD was equivalent to 3.23 GHC in January while in August 1 USD was equivalent to 4.31 GHC. This example demonstrates that the foreign exchange rates fluctuations can be significantly huge hence must be taken into account in an evaluation. Also, in the medium to long-term, policymakers could use HTA findings to negotiate the prices of health technologies (which will factor in the fluctuations in foreign exchange rates) with manufacturers and suppliers as done in other countries. Under such arrangements, the prices of health technologies can be stabilised over a certain period. This means manufacturers will also bear some of the costs attributable to fluctuations in the foreign exchange rates.

Access to tamoxifen under the NHIS is inequitable, as Ghanaians who are taxpayers but are not registered under the insurance scheme do not benefit from it. Improvements in equitable access to tamoxifen through an increase NHIS coverage would lead to an increase in the net cost of tamoxifen and consequently require additional financial resources. Additional financial resources required are even higher when the current market price of tamoxifen is factored in.

For instance, a 12% increase in the NHIS coverage (that is 50% of the population covered) would mean an extra GHC 616, 385 (AUD 178, 752), which represent a 95% increase in the NHIS current expenditure on tamoxifen (assuming 100% reimbursement at market price). The NHIS would require an additional GHC 1,887,620 (AUD 547,410) (that is, GHC 2,542,471 (AUD 737,316) in total) to fund tamoxifen at the current market price for pre- and peri-menopausal women should the insurance coverage reach 100%. Therefore, it is important that as Ghana pursues its goal of universal health coverage under the NHIS, planning include a financial impact analysis.

Any changes in the epidemiology of breast cancer presentation in Ghana will have an impact on the net cost of tamoxifen to the NHIS. As it can be expected that increased awareness of breast cancer screening will be followed by an increase in early detection and treatment, the number of early breast cancer cases will outweigh those of advanced breast cancer. However, modelling such changes did not have a big impact on the net cost of tamoxifen in this study, because the acquisition price of tamoxifen was the major driver of the net cost to the NHIS. In addition, the net cost was not affected by the stage of breast of cancer under the assumption that the prevalence rate remains the same even with changes in the epidemiology of breast cancer such that the current number of advanced breast cancer cases is replaced by early breast cancer cases. The minimal increase in the net cost is due to an increased frequency of follow-up visits by those with early breast cancer compared to those with advanced breast cancer per the treatment protocol used in Ghana (advice from a clinical expert).

On the other hand, in the real world, increased detection of early breast cancer cases would improve survival and increase the prevalence of breast cancer compared to the current situation where most patients do not survive due to the late detection of their cancer. Accordingly, more resources would be needed to fund tamoxifen. However, costs likely to be saved from early breast cancer treatment and the increase in survival rates of early breast cancer patients provides

an incentive to the Ghanaian decision maker to promote services that increase the early detection and subsequently, early treatment of breast cancer.

Exclusion of palliative care services that are needed for the care of end-stage breast cancer patients have led to an under estimation of the net cost of tamoxifen to the NHIS as demonstrated by the scenario analysis conducted in this study. This implies that more resources will be needed to fund tamoxifen should palliative care services be provided by the health system for advanced breast cancer patients.

The strength of this study is that it used local cost data to estimate the financial implications of funding tamoxifen under different scenarios. However, it is limited by the reliance on the input of one Ghanaian clinical expert to estimate resource use. Other assumptions underlying the analysis could have also led to either over or under estimation of the financial implications of tamoxifen. However, these were addressed by undertaking sensitivity analysis on a number of parameters and under different scenarios.

9.5 Conclusion

The chapter has presented the financial implications of funding tamoxifen to the NHIS budget under different scenarios. Currently, there is a gap between the cost of tamoxifen and what is reimbursed by the NHIS, with patients bearing the difference in costs. The fluctuations in foreign exchange rates are a major cause of this difference, hence the importance of factoring these into HTAs conducted in Ghana. The cost of funding tamoxifen for the hormonal treatment of pre- and peri-menopausal Ghanaian women would rise if NHIS coverage was expanded.

An increase in the prevalence of breast cancer will also increase the net cost to the NHIS. As a number of parameters affect the net cost of tamoxifen to the NHIS, it is important that in future planning, the NHIS consider these to ensure the sustainability of reimbursing tamoxifen.

Furthermore, even though the data used for this analysis was suitable for Ghana, investments would have to be made in data management such as consolidating existing data sources while new data are collected.

10 DISCUSSION

10.1 Introduction

HTA is a recognised systematic method of assessing the effectiveness, safety, and cost effectiveness of a technology, and the financial implications of reimbursing it to the payer. The use of HTA is widespread in developed countries and include the development of standard guidelines, recommendations regarding the reimbursement of drugs and medical devices, price negotiation and the selection of services for insurance benefit packages. The limited use of HTA in developing countries has been attributed to several factors including affordability, lack of human capacity and data availability.

The challenges of the Ghanaian health system, most especially in respect to methods used to select health services and medicines reimbursed under the NHIS that promote the financial sustainability of the health system, have led to the country's pursuance of HTA methods. A pilot study that adopted a model from the UK demonstrated that costs can be saved when HTA is used to inform guidelines for the treatment of hypertension. Subsequently, the newly formulated national medicines policy recommends the use of HTA for making decisions on essential medicines and coverage by the NHIS, with a particular focus on new and expensive health technologies. However, these were not supported by evidence on the feasibility of conducting and using HTA formally in the health system taking into account the challenges in the Ghanaian setting. The research conducted in this thesis therefore sought to provide this evidence to inform the planning and institutionalisation of HTA in Ghana.

The main findings from the research conducted for the thesis are summarised in section 2, and its limitations discussed in section 3. This is followed by a discussion of the findings in relation to literature on HTA in developing countries. The feasibility of Ghana adopting and using HTA, the available models and alternatives to HTA are also presented. Policy implications

suggested by the research findings will be discussed as will the contribution to the existing literature. The future research possibilities are also presented along with concluding remarks.

10.2 Key messages

In Chapter 2, a review of the current evidence regarding the types, uses and methods of HTA was carried out. HTA practices and uses in various health systems were examined to assess their applicability to the Ghanaian health system. Although the HTA framework is consistent across countries, the methods used are context-specific. Thus, there is no definitive way of conducting HTA. An approach derived from the context in which the outcomes of the HTA will be used is important as this is likely to directly or indirectly affect its use for decision-making and subsequent impact. With regard to the use of HTA to inform decisions, the literature review revealed that the use of and relative importance attached to HTA methods is determined by users' knowledge and understanding, and how the user perceives its benefits, which in turn is dependent on the individual's role and the decision-making context.

Chapters 3 and 4 reported the results of field-based research which assessed the decision-making context and practices of the Ghana health system. The awareness of clinical health workers regarding health decision-making processes in Ghana and their overall perception of what and who should be included in the process was presented. The current decision-making process was perceived as unfair and driven by politicians and political considerations. Health workers' perception of the current decision-making process was contrary to their preferred approach. They recommended that decisions should be based on maximising the wellbeing of the patient and population, and not on economic issues and political considerations. Their lack of recognition of economics as a relevant decision-making criterion is expected to have a negative impact on their acceptability and implementations of policies and recommendations made from HTA appraisal results.

The findings of Chapter 4 showed national and district decision makers in Ghana currently consider certain factors for making decisions such as patient and population welfare and health outcomes, but are open to other decision-making practices that are transparent and take the economic implications of decisions into account. Chapter 4 further examined the knowledge and attitudes of decision makers and researchers towards HTA. The study revealed a paucity of knowledge of HTA among decision makers and researchers. It also presented what they anticipated as barriers to the adoption of HTA and recommendations to address these. A major barrier was human and data capacity to conduct HTA. Some key recommendations in this study focused on building human and data capacity, legislating HTA for its mandatory use and involving all relevant stakeholders in HTA processes.

An investigation of the available data and human capacity in Ghana for HTA adoption was presented in Chapter 5. A systematic review of economic evaluation studies conducted in Ghana showed that studies were of good quality, broad in scope, but limited in quantity. The methodological approaches used were varied, hindering their usefulness in decision-making should a decision maker seek to prioritise any of the interventions evaluated in these studies. The chapter also found the human capacity available to conduct and train others in the use of HTA methods were limited. The findings suggest that human and data resource capacity needs to be developed for HTA in Ghana.

Chapters 6-9 constituted a series of studies in which tamoxifen for the hormonal treatment of breast cancer was used as a case study in order to assess the feasibility of HTA in Ghana. This included the transferability and generalisability of data from other countries to the Ghanaian context. Chapter 6 presented the rationale for the choice of tamoxifen, and a review of existing economic evidence to assess the transferability to the Ghanaian setting for HTA appraisal. As none of the studies was transferrable, a systematic search was conducted to identify appropriate data to conduct a new HTA. A limited amount of appropriate data was identified, particularly

in relation to the efficacy of tamoxifen, however none were specific to Ghana. The limitations of the unavailability of country specific data and limited amount of direct evidence on the comparators for this study were addressed by transforming the data identified for use in the Ghanaian context in Chapters 7 and 8.

The data identified in Chapter 6 were transformed and used in Chapter 7 to build a Markov model to evaluate the cost effectiveness of tamoxifen for the hormonal treatment of early breast cancer among pre- and peri-menopausal women in Ghana. In the absence of data required to populate an "ideal" model structure, a simpler model structure with fewer health states was used in the evaluation. Subsequently, the study examined the effect of model structural uncertainty on the estimated ICER. This situation is anticipated when conducting HTA in developing countries where data are limited and there is reliance on data from developed countries. The differences between these settings such as different treatment protocols and availability of resources have an impact on the design of the model structure for the evaluation as it must be plausible. Three alternative health outcomes were used in the analysis and were found to have an impact on the estimated ICER and subsequently the cost effectiveness of the technology. When used as the outcome, QALYs (the base case) resulted in a lower ICER, compared to life years saved and DALYs averted. The difference in the ICERs estimated using QALYs and DALYs contributes to current discussions in the literature on the differences in these measures and their impact on decision-making (76, 89, 91). The thesis proposes the use of QALYs among these three outcome measures as it considers both the quality and the quantity of life years extended by a health technology. The cost of tamoxifen was the key driver of the ICER. The ICER was not sensitive to a change in the model structure. Extending tamoxifen therapy beyond five years (to ten years) increased the incremental cost, but not the QALYs gained, resulting in an overall increase in the ICER.

A second model was developed to assess the cost effectiveness of tamoxifen among pre- and peri-menopausal women with advanced breast cancer (Chapter 8). The clinical effectiveness data on tamoxifen identified for this cohort of women were not applicable to Ghana because of the differences in available treatment and protocols. Due to lack of a direct clinical effectiveness data, data from two arms of two different studies, with no common comparator, were used to populate the second model. The limitations of this method were tested in a sensitivity analysis. The probability that tamoxifen would be cost effective compared to no tamoxifen for the hormonal treatment of advanced breast cancer was lower compared to early breast cancer: 0.51 versus 0.80. Thus, tamoxifen is highly cost effective for the treatment of only early breast cancer among pre- and peri-menopausal women in Ghana.

For both models, even though there were many RCTs assessing the effectiveness of tamoxifen for the hormonal treatment of pre- and peri-menopausal women with breast cancer, those directly relevant to Ghana were limited. This was due to exchangeability issues such as different comparators, population characteristics (such as age), cancer stage at presentation, and prior treatments used in developed countries (where clinical trials were conducted) which are different from Ghana. Utility data identified were not specific to Ghana or any African country. A clinical Ghanaian expert was relied upon to estimate resource use and associated cost of tamoxifen therapy. Further the market price of tamoxifen was found to fluctuate due to the instability of the foreign exchange rate (as it is imported).

Chapter 9 presented a detailed assessment of the financial impact of the cost of tamoxifen therapy on the Ghana NHIS. Patients currently incur out of pocket costs because reimbursement provided by the NHIS does not cover 100% of the cost. Thus, additional funds will be needed to fill this gap. There is inequitable access to tamoxifen in Ghana due to the proportion of the population currently covered under the NHIS. To remove this barrier to tamoxifen and other health services, the financial barrier due to insurance premiums and

registration will have to be removed. Another approach would be educating the populace on the importance of insurance: access to needed healthcare without impoverishment due to catastrophic health expenditures, and incentivising them to enrol in a health insurance scheme. On the other hand, any increase in NHIS population coverage and/or the price of tamoxifen will increase the financial burden on the NHIS. However, changes in the proportion of women diagnosed with early or advanced breast cancer will not increase the costs of tamoxifen to the NHIS if the current prevalence rate is maintained.

10.3 Limitations and challenges

There are other approaches/methods to priority setting discussed in the literature other than HTA that could have been explored. However, this discussion has focused on the use of HTA for resource allocation only. Other methods, which may be applicable in Ghana, include program budgeting and marginal analysis (PBMA), MCDA and the Equity Oriented Tool Kit (EOT), which are discussed under section 10.5.3.

The systematic review conducted in Chapter 5 of this thesis was limited by the fact that only one person (PhD candidate) independently conducted the review. The thesis recognises that best practice would require a second independent reviewer. However, this could not be done as employing a second reviewer was not feasible within the resources available as a PhD candidate. In addition, the PhD candidate wanted to maintain independence in producing research output for this thesis. the review was also limited by the fact that the quality assessment tool did not have criterion for assessing the quality of data used for the economic evaluations.

The limited use of HTA in developing countries has been attributed to the lack of data and human capacity. The inability to transfer economic data from one jurisdiction to another and decision makers' inability to interpret those results highlight the difficulty in using HTA

findings from other settings. This thesis presented an opportunity to assess the implications of these challenges on the formal introduction of HTA for decision-making in Ghana using tamoxifen for the treatment of breast cancer among pre-and peri-menopausal women as a case study.

As with most economic evaluations conducted in these settings on technologies that have not undergone clinical trials in the setting, lack of data was a major limitation. In particular, the non-existence of utility estimates, non-applicability of clinical efficacy data (particularly direct evidence) and lack of data on resource use was a big challenge that needed to be overcome. The research conducted in this thesis explored methodological approaches that could be used to address these challenges, and these approaches can be emulated in similar contexts.

However, the use of a single case study to assess the transferability of data from other countries to Ghana for HTA is a limitation as it may not be a true reflection of what is the case for other health technologies. Perhaps, using two different health technologies in a case study (for example one for treatment and the other for prevention), would have allowed for identification and comparison of potential methodological challenges. However, the scope and duration of the thesis permitted only one case study. From the findings, it can be argued that the technology selected for the case study has similar characteristics to other technologies that are likely to be funded in Ghana and therefore represents a highly relevant example. The case study is also generalisable to other settings with similar characteristics to Ghana.

This thesis did not consider equity in the HTA appraisal by valuing health gains by different population groups' differently. The importance and implications of weighting utility values differently for different population groups remains contentious in the literature and is still under exploration (294).

10.4 Research on HTA in developing countries

There is a growing body of literature regarding HTA in developing countries, however most studies have focused on evaluating the cost effectiveness of a health technology as demonstrated in the systematic review of economic evaluation studies done in Ghana. These studies did not assess the feasibility and methodological challenges associated with conducting them; nor did they investigate the health system constraints associated with adopting and using the results.

Nonetheless, a few studies have examined the feasibility of using HTA and its methods in specific contexts. For example, a study conducted in Thailand assessed the feasibility of using economic evaluation to inform the benefit package under the Thai system of universal health coverage (295). The study investigated the availability of economic evaluation studies for decision-making and decision makers' attitude and knowledge of economic evaluation using findings from a CEA conducted to evaluate treatment options for end-stage renal disease and gallbladder stone disease as a case study. The study reported a limited number of economic evaluations, which used different methodological approaches. Further, they identified that decision makers lacked understanding of these economic evaluations, which is similar to the findings of this thesis. They found that most decision makers in Thailand did not support the use of economic evaluation on its own for decision-making because it did not take into account other factors such as equity, protection of the populace against catastrophic health expenditure and social solidarity. The study concluded that the use of economic evaluation for decision-making in Thailand could be improved if methods of conduct were standardised, other factors such as equity were taken into consideration, evaluations were responsive to the needs of decision makers and stakeholders were educated about economic evaluation and its relevance to the health system. The factors identified in this thesis to promote HTA use are comparable to that recommended for Thailand.

Castro (296) also investigated the feasibility of incorporating HTA findings into the decision-making process of the Columbian health system. In this study, he examined the attitude of decision makers towards HTA by using the CUA of two treatment strategies for severe haemophilia A as a case study and finally used these findings in a multi-criteria decision analysis (MCDA) to answer his study objectives. He concluded that it was possible to incorporate HTA in the decision-making process when barriers identified by decision makers such as lack of quality data, financial support and local capacity were addressed. The barriers to HTA identified by decision makers in the Colombian study are similar to those reported by decision makers in this thesis.

Even though the two studies described above assessed the feasibility of using HTA methods in health systems, their methodological approaches were different to that used in this thesis. A major strength of this thesis compared to these studies was that, in addition to what the two studies described above did, this thesis also assessed the methodological challenges associated with transferring data from developed countries to developing countries for use in HTA. These additional findings from this thesis contributes to the literature on HTA in developing countries.

Other studies have also looked at characteristics of health systems that can promote the introduction and use of HTA in emerging economies. For example, Towse et al. (297) hypothesised that the resources available within a country (using GDP per capita as a proxy) and the characteristics of the decision maker (for example, government or physician) responsible for healthcare funding decisions are likely to directly inform the establishment and use of HTA for decision-making, and subsequently inform the focus and breadth of HTA activities. In their study, three emerging economies; Brazil, China and Taiwan were used to test this hypothesis. They concluded that HTAs were more likely to be institutionalised when the GDP per capita of the country was higher, government is the payer and there is an incentive

to promote efficiency in the health system. Based on their study, Towse et al. (297) proposed a conceptual model to assess health systems for the introduction and use of HTA, which was used by Babigumira et al. (298) to investigate the use, conduct and challenges of performing HTA in some selected developing countries[42]. They identified a strong positive relationship between HTA and the capacity and attitude of the decision maker responsible for funding decisions but a moderate relationship between HTA and GDP per capita of the countries surveyed. From these findings, it can be argued that other factors, other than those proposed by Towse et al. (297), such as the technical capacity and attitude of decision makers towards HTA that was assessed in this thesis contribute to the introduction, performance and successful use of HTA by developing countries.

The knowledge and attitudes of decision makers in Ghana towards the use of HTA methods was explored in Chapter 2 and findings were integrated into Chapter 4. In summary, just as identified in this thesis, decision makers from other developing countries reported that lack of human, data and financial resources were the major barriers to HTA use in their settings (2, 5, 6, 18, 119, 120, 130, 152). Decision makers' lack of knowledge of HTA methods and their potential benefits to the health system and lack of political will were also cited as a hindrance to its acceptance and use (5, 119, 120), which is similar to the findings of this thesis. Some of the common measures suggested by decision makers in this thesis and in those studies to promote the use of HTA methods are developing human capacity, collation and management of data, making funds available for HTA, education about HTA, and getting the support of stakeholders. In addition to these, decision makers interviewed for this thesis also reported the

[42] These countries were Afghanistan, Angola, Bangladesh, Democratic Republic of Congo, Dominican Republic, Ethiopia, Guatemala, Jordan, Kenya, Liberia, Lesotho, Mali, Mozambique, Namibia, Rwanda, South Sudan, South Africa, Swaziland and Vietnam

necessity of a legislative requirement or policy to require the conduct of HTA, stakeholder involvement in all HTA processes and dissemination of findings.

10.5 Policy implications

As discussed in Chapter 1, some of the progress made by Ghana towards the formal use of HTA for decision-making is having a policy statement (included in the new Ghana medicines policy) on the use of HTA for decisions on medicines selection and formulating treatment guidelines. However, what this policy document failed to do was discuss how and when the policy will be implemented and the type of HTAs that will be undertaken. In addition, this policy statement was not based on evidence on the feasibility of conducting and using HTA in Ghana. Nonetheless, the findings from this thesis has provided evidence on the feasibility of HTA in Ghana. This thesis has shown that despite several limitations, it is feasible to conduct an HTA in Ghana. However, to effectively introduce and use HTA in Ghana as stated in the GNMP, the following policy implications on the acceptance of HTA, its conduct, focus and model of appraisal, will need to be considered.

10.5.1 Acceptance of HTA

In Ghana, even though decision makers expressed an interest in using HTA to inform decision-making, clinical health workers, who are the implementers of HTA findings, did not recognise the importance of integrating the results of health economics studies in the decision-making process. This, together with the limited knowledge of HTA, has the potential to hinder the introduction and successful use of HTA in the Ghanaian health system. Therefore, before the formal introduction of HTA as a decision-making criterion in Ghana, it is necessary to create awareness and educate all stakeholders, including policy makers and health workers, in its methods, uses and importance.

In addition, legitimate questions raised by decision makers involved in the study will have to be addressed if HTA is to be successfully used in Ghana. These questions include: where to locate the HTA organisation? Who should carry out the assessments? What evidence will be considered in the appraisal process? Who should make the final decision? Adopting a legal framework that addresses these questions and mandates HTA use will promote its acceptance, use and diffusion across the health system.

10.5.2 Conduct of HTA

This study has provided an opportunity to identify some resource and methodological challenges associated with HTA and how they can be overcome, which are discussed below.

Human resource capacity

Evidence suggests that inadequate human resource capacity is a major barrier to the conduct and use of HTA (4, 18, 20). In Ghana, capacity was found to be limited. A possible explanation is that because HTA is not currently used, there is no demand for the required knowledge and skills, and hence training institutions are not incentivised to recruit individuals with such skills to supply the necessary education. In addition, some people who have expertise in HTA may not have been identified. For instance, there may be people in disciplines other than health, who may have skills in conducting economic evaluation and other methods of HTA, that were not captured in this study. Therefore, the extent to which human capacity is limited is unclear and will require further exploration in the Ghanaian context prior to the adoption of HTA. Such knowledge will guide policy makers in developing a human resource plan to address the capacity deficiencies identified in this thesis. In the interim, human resource capacity can be developed through collaboration with other countries that do have capacity to conduct HTA, by sending people to such countries to develop their capacity to conduct HTA to become future trainers in Ghana in the medium to long-term.

Data

The data available for HTA in Ghana is limited and needs to be enhanced. In the meantime, Ghanaian researchers will have to rely on effectiveness and utility data from other settings to conduct most evaluations. Evaluations conducted with international data may not be perfect; however, there is sufficient validity in the analysis once measures are taken to address exchangeability issues through the transformation of international data to be applicable to the context where evaluation is conducted. This approach however comes with its own limitations, which have been pointed out by this thesis and the methods available to overcome or mitigate them also discussed. Using tamoxifen as a case study highlighted the common problems anticipated to occur when, in the absence of local specific data, data on the effectiveness and safety of a technology from clinical trials conducted in other countries are used to populate a model. The differences in the clinical treatment algorithm between developed country settings where these trials are conducted and developing country settings is an example of this difference. To address this, pharmaceutical companies could be encouraged to consider the probable differences in treatment protocols and resource use between developed and developing country settings. Including developing countries in clinical trials would provide researchers with the data necessary to conduct an evaluation. However, it is worth noting that companies are unlikely to want to conduct clinical trials in countries that prefer, or can only afford, unpatented health technologies. Another way of making these kinds of data usable and available for researchers from developing countries is to establish a research group (such as the EBCTG) which would aggregate existing data on health technologies in a meta-analysis, with a focus on their use in developing country settings where possible.

To strengthen the availability and use of quality data for HTA, a national data repository that collates all the data relevant for such evaluations would have to be created and regularly maintained. This could be created through a collaboration between academia and the Ministry

of Health, with one or the other tasked with its maintenance. In addition, a global repository of resource use and cost data could be created to support developing countries such as Ghana, in assessing such data which are limited in their countries. Currently, there exists a Global Health Cost Consortium, but it focuses on only improving resources to estimate the costs of tuberculosis and HIV programs in low and middle-income countries. As an alternative to creating a new global cost repository, this consortium could be expanded to cover other non-communicable diseases such as cancers. This will improve the use of quality and context-specific data on resource use and cost for the conduct of economic evaluation in developing countries.

The thesis also revealed a major constraint in terms of the lack of data on resource use. It was necessary to rely on expert advice for inputs regarding the utilisation and costs of various aspects of treatment for breast cancer. If evaluations are to be consistent in terms of results, it will be necessary that treatment protocols used in Ghana be documented together with information about the associated resource use. Nonetheless, in the short to medium term, expert input will be essential for conducting HTA in Ghana, while the necessary data are collated and made accessible to researchers. The thesis therefore proposes that a standing panel of clinical experts and other relevant stakeholders be formed who would supply inputs into HTA appraisals when needed. The composition of this panel could mimic the population, intervention, comparator and outcomes (PICO) advisory sub-committee (PASC) of the MSAC of Australia. The PASC consists of epidemiologists, consumer representatives, health economists, public health experts and clinical experts. Their main role is to confirm the PICO for a health technology that subsequently informs the model structure and parameters for the HTA (299).

Methodological approach

It is important that Ghana develops a country specific methodological guideline for the conduct and reporting of economic evaluation studies eventually. In the meantime, it could adapt a current guideline for use in the short term. This would help address the differences in methodological approaches and promote consistency in economic evaluation results as well as their use. Some key areas to consider in guideline development include: choice of effectiveness outcome, perspective of analysis, unit cost, choice of comparators and cost effectiveness threshold (CET), which are discussed below.

The case study has highlighted important differences in the results when QALYs or DALYs are used as the outcomes of an economic evaluation. Therefore, the choice made about which health outcome measure to use will have implications for the cost effectiveness of the technology, and subsequently the decisions made. This thesis argues that any decision about which outcome measure to use in economic evaluation will need to take account of the advantages and limitations of each. Hence, the thesis proposes the use of both measures wherever possible, to provide the decision maker with evidence on the implications of each measure on their decision. However, country specific population norms regarding the quality of life (utility weights) and subsequently disease specific utility and disability weights would have to be created so outcome measures are reflective of Ghanaians' preferences.

A decision will have to be made on what perspective of analysis to adopt for economic evaluation. Adopting a payer perspective as required by most HTA agencies around the world may not be suitable for Ghana in all situations. This is because, as demonstrated in the thesis, some conditions that require patients and families to incur costs because of the shortcoming of the health system may warrant that a societal perspective is used. However, should these services be provided in the Ghanaian health system in the long-term, a payer perspective could be adopted instead. In addition, a societal perspective considering out of pocket costs and costs

of productivity loss by patients and families can change the results of an analysis: from cost effective to not cost effective, depending on the extent on the costs as demonstrated in this thesis. On the other hand, improvement of health or health gains through an intervention would improve productivity and once the productivity gain is included in an evaluation as health gains, the cost effectiveness of an intervention can improve. For example, an intervention that is not cost effective can change to become cost effective when productivity gain from the intervention is imputed in the evaluation as health gains. Nonetheless, adoption of a health technology that has been appraised as cost effective is expected to be low in instances where patients and families need to pay additional out of pocket costs to access it. Thus, there will be a difference in the financial impact estimated for the health technology and what is actually spent depending on the number of people who would eventually access it. Also, in instances where the differences in uptake between different population groups due to financial barrier to access is taken into account in the evaluation, a health technology estimated to be cost effective may become less cost effective as a result of reduction in the overall health benefits.

In addition, the country would also have to decide which costs to include in each perspective of economic analysis, in addition to what is considered in a standard economic evaluation. For example, a health system perspective may consider the costs to implementing the intervention which include health system challenges such as a shortage of trained health workers. Lack of consideration of such costs is a limitation to the general approach to economic evaluation where opportunity cost is taken as the going payment rate. However, it is important that appropriate opportunity costs be identified and included in an economic evaluation, even though this may be a challenge in cases of severely limited supply of health resources.

Another issue to consider is the effect of unstable foreign exchange rates on costs, specifically in relation to imported health technologies. Reliance only on the current NHIS reimbursement price list for HTA is likely to underestimate the cost effectiveness of a health technology, its

financial impact on the health budget and consequently skew the decisions made based on such information. Because Ghana imports many drugs, fluctuations in the foreign exchange rates result in unstable drug prices. Hence, at a particular point in time, the NHIS reimbursement price list may not reflect the true market value of the health technology. Therefore, it is necessary that economic evaluations and HTA conducted in Ghana account for these differences either in a base case or in sensitivity analysis to provide policy makers with up-to-date reliable information for decision-making.

An additional way of addressing the above issue is to have a price list reflective of the current market value for a set period of time. Drawing on the findings of this thesis, this could be achieved by using HTA findings to negotiate prices of medicines and other technologies, which would in turn lead to cost savings to the government. Currently, the reimbursement price of medicines, which constitute more than 60% of the NHIS expenditure, is driven by the market price of medicines, which fluctuate due to unstable foreign exchange rates. Thus, through price negotiation with the manufacturer, the price of medicines could be stabilised based on the reimbursement price agreed for a number of years irrespective of the fluctuations in foreign exchange rates. This will in turn promote consistency in HTA in using a common reliable source of cost data that will not be affected by changes in the foreign exchange rates over a certain period.

To ensure consistency in the estimation of costs associated with resource use in economic evaluations, lessons can be learnt from countries such as the UK and Australia where manuals are developed for use by researchers and evaluators. In Australia, the Department of Health has developed a manual that outlines the sources of unit costs of drugs, medical devices and medical and health related services to be used by pharmaceutical companies for PBAC submissions (300). The manual is updated regularly to reflect current prices of health technologies and services. The UK also has a data repository on unit costs of health and social

care which is compiled yearly by a research unit in an academic institution, for use by researchers (301).

Differences in clinical practice hinder adoption of HTA findings from other settings and transferability of economic evaluations and clinical trial results from other countries to Ghana. This further affects the data available for economic evaluations as well as comparators. Therefore, this thesis advises that the methodological guideline should make provisions for using 'do nothing' or basic standard support as a comparator in every evaluation as already observed in the economic evaluation studies from Ghana. This will address situations where available comparators are not applicable to the Ghanaian setting as demonstrated in this thesis. In addition, the methodological guidelines should make provisions for adapting as well as exploring other innovative ways of conducting an economic evaluation. This is because there may be instances, where written and/or recommended guidelines may not be applicable to a particular decision problem. For example, even though there are existing guidelines for data transferability for economic evaluation, such as developed by the ISPOR task force for good research practice, an evaluator may have to consider other factors when faced with issues not discussed in this guideline as revealed in this thesis and discussed under section 8.4.5 thereof. This may apply to other existing good practice guidelines for economic evaluation and HTA. Thus, it will be important to update continuously the methodological guidelines based on new lessons learnt.

Ghana, as other developing countries, does not have a country specific WTP threshold that can be used to determine the affordability of a health technology (302). In the past, researchers have examined the cost effectiveness of health technologies evaluated in Ghana using the WHO

cost effectiveness threshold[43], however this has since been withdrawn due to criticisms of its lack of theoretical foundation. Therefore, it is important that Ghana determine the WTP threshold against which decision makers can judge the cost effectiveness of a health technology for funding.

Cost effectiveness threshold represents what a society is willing to pay for a health gain. This estimate is the value of consumption that the society is willing to give up, either from the health system or other government sector, to gain a QALY or avert a DALY. Two main conceptual perspectives underpin the estimation of a CET in the literature. While one perspective argues that the threshold should reflect the opportunity cost of displaced health care or other government services given budget constraints, the other argues that it should be reflective of the value placed on QALYs by the society (that is, society's WTP/QALY for a health technology that extends or saves lives) (8, 303, 304). The CET values estimated using the principle of opportunity cost is lower compared to those estimated using the society's valuation of QALY (304). In other instances, some studies have used the value of an already funded health technology as the CET under the assumption that the new technology will displace the existing technology (305). This approach is only applicable when there is a fixed budget for healthcare and new spending is impossible. Ghanaian decision makers would have to decide what CET means in terms of its implications on funding: either being an opportunity cost displaced from the health budget or finding new funds for a new technology. The current funding arrangements are not clear on what is and what can be allocated to healthcare. However, since HTA seeks to provide decision makers with information for priority setting within a constrained budget, this thesis used a CET estimated by Wood et al. (282) which considered the opportunity cost (estimated from a UK study) and estimates generated from the

[43] It states a health technology is highly cost effective if the ICER/CER is less than the per capita GDP of a country, is cost effective if ICER/CER is less than three times the per capita GDP of the country and not cost effective if the ICER/CER is more than three times the per capita GDP of the country.

relationship between value of statistical life (WTP to reduce mortality) and the GDP of Ghana. Therefore, irrespective what CET means to Ghanaian decision makers, this thesis recommends that they adopt the CET by Wood et al. (282) in the short term. However, in the medium to long-term, the thesis recommends that Ghana uses a the approach used by Woods et al. (282) where a Ghanaian specific opportunity cost in healthcare is derived and used in the same way to estimate a Ghana-specific CET. This is relevant as there are other opportunity costs peculiar to Ghana and most developing countries that were not captured by Woods et al. (282). For example, most developing countries are heavily reliant on donor funding for healthcare delivery. Hence, it will be important to estimate the opportunity cost of substituting donor funding for government funding. The opposite is also important most especially as some developing countries such as Ghana are currently transitioning from a low middle-income country to high middle-income country, which means a reduction in financial support received from donor agencies.

What should HTAs focus on?

As demonstrated in this thesis, HTA appraisals used in Ghana will need to be based on country specific characteristics, as adopting findings or models from other countries may misinform decision makers due to the reasons discussed in chapters 6, 7 and 8.

In a resource-constrained health system, decision makers will need to prioritise which health technologies to appraise, for example, treatment interventions versus drugs, and for drugs, generic versus patented. This will also inform the type of HTA to pursue and the type of evaluation to be conducted if a full HTA appraisal is to be done. For example, a cost minimisation analysis would be appropriate for HTA in cases where generic drugs are appraised, so that the medicine with the lowest cost is included for funding by the NHIS. The same is likely to be the case for other interventions with established and equal outcomes. For

new interventions such as for public health and other new treatments for conditions, which may have no treatment available, a full economic evaluation will be necessary.

Even though the current medicines policy in Ghana indicates that HTA appraisals will focus on expensive health technologies such as new vaccines, this thesis argues that policy makers should shift their focus considering the resource limitations and the overall aim of sustaining the NHIS and health system. The thesis proposes that it would be more appropriate in the short to medium term for full HTA appraisals in Ghana to focus on assessing health technologies where effectiveness and/or outcomes have been established as being equal, but where costs differ, to choose the least costly one for reimbursement. In the case of medicines, as shown in this study, evaluating generic drugs to ensure that the least costly in terms of financial impact on the health budget allows progress to be made immediately. The price drop when generics of patented medicines become available makes their funding more feasible under the NHIS. A focus on health technologies such as generic drugs and off-patent technologies will also address the national health policy objective to improve efficiency in the health system and ensure the financial sustainability of healthcare delivery. This is not to say that HTA appraisals should not be undertaken for new health technologies. However, decision makers should bear in mind the financial implications of funding new technologies. As this thesis has demonstrated, a newly-patented health technology is highly unlikely to be cost effective and affordable considering the WTP of Ghanaian decision makers and financial resources currently available for health delivery.

Again, policymakers will have to consider financial equity (that is financial access) in the context of HTA appraisals. Even though this study did not discuss the financial equity and legal implications of adopting tamoxifen, it showed that under the current NHIS arrangements, less than half of the population (pre- and peri-menopausal women likely to have breast cancer) who needed tamoxifen were receiving it. Health workers and decision makers were also of the

opinion that current health decisions were inequitable; future HTA processes should consider equity in order to reinforce its relevance in Ghana. Another issue worth deliberating by Ghanaian policymakers is if the HTA appraisals conducted for the NHIS will be applied to other private health insurance packages in Ghana. This is important as different pricing and funded health technologies for the same indication promotes financial inequity across different insurance schemes. Paying out of pocket costs to access some health technologies as demonstrated in this thesis (due to the differences in the market prices and NHIS reimbursement prices) can deter some people who are insured under the NHIS from accessing those technologies. This will result in inequity of access across the insured NHIS population. Thus, it is necessary that measures are taken by the government to remove additional out of pocket payments made by those insured under the NHIS.

HTA models for exploration

Should policy makers embark on HTA, they would have to decide which HTA model to adopt. Different models are used by different HTA agencies and are mostly driven by the decision-making context in the country. These models include industry-sponsored submissions that are evaluated by academic researchers commissioned by the responsible decision-making body such as the case of the PBAC of Australia, NICE of England and Wales, and HIRA of South Korea (109, 112, 117). Under this model, industry conducts the HTA that is appraised by researchers, and industry bears most of the cost associated with the appraisal. However, pharmaceutical companies only choose to make these submissions when they are likely to benefit, as in the case of new medicines. Thus, this model is not likely to be applicable in the Ghanaian context if the focus of HTA is on generic medicines in the short to medium term. A different approach is observed in New Zealand where evaluations of industry-sponsored submissions are carried out by HTA and decision-making body, PHARMAC (115). Perhaps, some form of exclusivity such as that observed in New Zealand, where an annual tender process

is run by PHARMAC for pharmaceuticals no longer under patent and where the winning bidder is allowed to be the sole supplier of the medicine for a fixed term (usually three years) (115, 306). This model could be emulated in Ghana and other developing countries.

Another HTA model in current use is the process that involves government commissioning research organisations to conduct an HTA appraisal of selected health technologies (selection may be with/without the input of other stakeholders). This HTA process is used by the HITAP of Thailand, MSAC of Australia, CENETEC of Mexico, NICE of UK, CADTH of Canada, NIHTA of Taiwan and the Agency of Care Effectiveness of Singapore (14, 104, 109, 110, 113, 118, 307). The researchers conducting the appraisal could be in an academic institution, part of an HTA body or consultancy firm either inside or outside the country. To address the issue of limited human capacity, Ghana could issue tenders internationally for conducting HTA, as seen in Singapore where international experts are contracted to either conduct an HTA or review an HTA conducted by researchers from their HTA agency (307).

10.5.3 Alternatives to conducting a full HTA

Other types of HTA such as mini-HTAs and rapid reviews that are not data and human resource intensive compared to a full HTA are worth exploring in the short to medium term before the Ghanaian health system starts conducting full HTA appraisals in the medium to long-term. Alternatives to HTA like PBMA, MCDA, Equity EOT and KNOW ESSENTIALS have also been proposed for use in priority setting in settings with limited capacity, and these should also be explored in Ghana. However, with the exception of MCDA (36), the feasibility of using the other approaches mentioned above in Ghana have not been done yet.

MCDA is a decision-making process that analyses a ‘health decision problem’ taking into account multiple factors/criteria that affect it. It has been applied to a range of health decisions including benefit-risk assessment, priority setting frameworks, shared decision-making,

prioritising patient access to healthcare, portfolio decision analysis and HTA (308). In the area of HTA, it has been suggested as a useful approach to incorporating other decision-making criteria beyond the cost effectiveness of a health technology, which is being explored by various HTA agencies (309-311). It however has some methodological challenges such as overlap between criteria and appropriateness of weights apportioned to criteria that require investigating (310). MCDA has been used to guide decision makers in making choices between different interventions considering factors other than HTA findings (296) and for the selection of interventions to be appraised using HTA for inclusion into an insurance benefit package (312).

PBMA also considers both economic and equity issues in resource allocation decisions in healthcare, and has been used internationally in countries such as Australia, New Zealand and the UK over the last three decades (313-316). PBMA is not based on economic evaluation. KNOW ESSENTIALS (317) and EOT (318) have similar characteristics to HTA, thus would require similar set of skills and data to conduct. In addition, while EOT focuses on equity issues, its weakness is the failure to estimate the financial implication of the technology to the health system. KNOW ESSENTIALS is also limited by the fact that it involves using findings from economic evaluations reported in the literature to make decisions, which is constrained by the inability to transfer economic evaluation results from one setting to the other as demonstrated in this thesis.

10.6 Contributions of thesis to existing knowledge

The findings of this thesis contribute to the literature on HTA and the knowledge needed to establish and use HTA in Ghana. First, this is the first study conducted in Ghana that examined the knowledge and attitudes of decision makers and researchers towards HTA (see Chapter 4). The study used in-depth interviews to explore this, providing rich data. The findings from this

chapter contribute to the relevant knowledge needed to develop policies and guidelines for HTA in Ghana.

Second, in assessing the resources available in the Ghanaian health system to support HTA, Chapter 4 adds to the literature on the factors used by decision makers in resource allocation. The results from Chapter 3, on the other hand, add a new dimension to the literature on factors to be considered for decision-making by examining the perceptions of health workers who implement policies about what factors should be considered and which stakeholders should make the decisions. Chapter 5 also contributes to the literature on the quality and quantity of economic evaluation studies in Ghana. It further investigated the available local capacity for HTA in Ghana, and is the first study to assess these important issues. These findings provide important information for formulating future health policies including the adoption of HTA in Ghana.

The HTA conducted using tamoxifen as a case study has revealed some potential challenges in terms of data availability and methods that are likely to be encountered as Ghana prepares for the formal introduction and use of HTA. Recommendations regarding how such challenges could be addressed provide necessary and useful information for decision makers. The HTA on tamoxifen for the HTBC also provides information about how the current funding arrangements for tamoxifen under the NHIS may be affected by the results of such an evaluation. The budget impact analysis demonstrates the usefulness of the results for future planning by the government of Ghana.

This thesis also contributes to the international pool of knowledge on HTA. Specifically, it contributes to the limited literature on HTA in developing countries. This includes the knowledge and attitude of decision makers and researchers towards HTA, a systematic evaluation of the quality and quantity of economic evaluations in a country and the assessment

of available human resources for HTA. The HTA on tamoxifen for the HTBC is the first to be conducted in an African setting. It also contributes to the limited evaluations of tamoxifen for the HTBC among pre- and peri-menopausal women. In addition, from a methodological perspective, Chapter 8 of this thesis contributes to the approaches that could be used to evaluate a technology when the sources available to estimate efficacy are extremely limited (in this case one arm of an RCT). It further contributes to the existing guidelines for the transferability of data for economic evaluation across jurisdictions, and makes recommendations for updating it.

Finally, based on the findings from the research undertaken for this thesis, a conceptual framework is proposed and recommended for countries planning to introduce HTA in their health system, to assess its feasibility to inform the planning and establishment of an HTA agency and/or process. This is because, this thesis and other studies have revealed that every country has specific characteristics and needs; hence, it is not advisable to wholly adopt HTA processes carried out in other countries. The conceptual framework is presented in Figure 10-1. The thesis recommends that before a country establishes and uses HTA for decision-making in any health system, it is prudent to assess the health system to establish its peculiar characteristics such as existing factors influencing decision-making, assess the knowledge and perception of potential users and producers of HTA, the available in-country technical capacity for HTA. To throw more light on the potential barriers and logistics needed for HTA, one or more case studies could be conducted. Findings from these studies will inform decision-makers on the processes and scope of HTA that could be embarked on in the country.

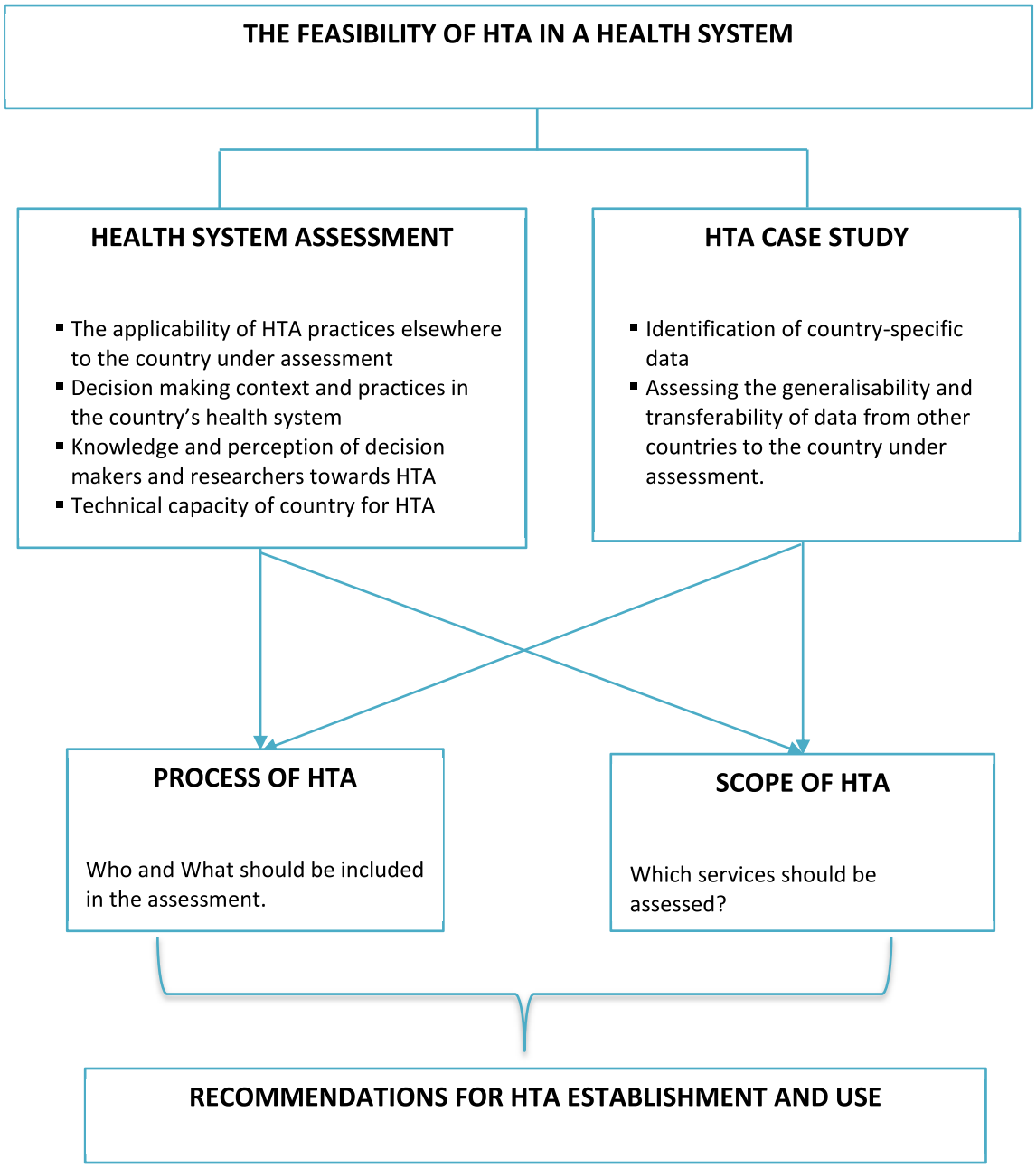


Figure 10-1: Conceptual framework for assessing the feasibility of introducing and using HTA in a health system for decision-making.

10.7 Future research

Several avenues for future research are suggested by results presented in this thesis. Future studies could explore the impact of HTA results on reimbursement decisions or the role of clinical guidelines compared to HTA tied to reimbursement decisions. Different approaches

available for priority setting (in resource allocation) could be explored in future research to assess their applicability and feasibility in the Ghanaian health system.

Further studies could be conducted to understand the reasoning behind the responses of clinical decision makers, especially their understanding of what a health economist does and the relevance of their inputs to decision-making in the health system. Also, future research can explore the knowledge of and perception of other stakeholders such as politicians, consumers and representatives of donor agencies about HTA and its use in the Ghanaian health system.

In addition, future studies could adopt a different methodological approach to assess the human capacity available to conduct and train others in economic evaluation and other HTA methods in Ghana. An example of such an approach would be to identify the number of Ghanaians affiliated with organisations known for health economics and economic evaluations such as HTAi, ISPOR and the African Health Economics and Policy Association. Once identified, they could be followed up in a survey to assess their skills for HTA.

Another area of future research is to conduct studies to derive utility values for the quality of life of the Ghanaian population. In the absence of country specific utility weights for health states of specific conditions, the utility values derived from studies conducted in other settings could be compared with the overall quality of life of a Ghanaian as a form of validation. This would form a baseline to conduct other studies assessing the quality of life of patients with specific conditions. In addition, beyond Ghana, a group of researchers could be convened to work on aggregating existing efficacy and utility data on health technologies that could be used by developing countries in conducting HTA to inform health decisions.

The cost estimates used in this model were derived with input from only one clinical expert. Future studies could estimate the resource use in breast cancer treatment and subsequent costs using data collected from the clinical setting. Costs incurred by patients and families can also

be extended to include the costs of terminal illness (palliative care) including care rendered by family caregivers and the cost of premature death due to productivity loss from the death of a patient. Other studies could be conducted using a similar approach to that described above to estimate the cost of illnesses of other health conditions for use in economic evaluation studies in Ghana.

It would also be useful to conduct another case study using a health technology recently introduced onto the market such as trastuzumab, to examine the availability of clinical effectiveness data relevant to clinical treatment protocols used in Ghana.

Furthermore, studies evaluating other technologies should be conducted with the particular focus of exploring issues relating to transferring data for economic evaluation from developed countries settings to developing countries settings, most especially, in the case when decision-analytic models are used. Decision-analytic models enables the researcher to synthesise treatment effectiveness data from other jurisdictions (including meta-analysis of international trials), utility data from a range of published literature and resource use data from either same setting or a different setting, for an economic evaluation. Therefore, this approach to economic evaluation is more applicable in developing country settings, which are usually not sites for international clinical trials, hence, would require to transfer data from one jurisdiction to the other.

Finally, a future study geared towards the introduction of HTA in Ghana should focus on developing a methodological guideline for economic evaluation in the context of the country and its health system, including inputs from appropriate stakeholders. This should be followed by a study to set a national WTP threshold to support and guide decisions made with HTA findings and recommendation in the Ghanaian health system.

10.8 Concluding remarks

This study has examined the systems and resources available to conduct HTA in Ghana. It also used a case study to investigate the transferability and applicability of data from other countries to Ghana for HTA. This research has identified resource and methodological challenges of HTA in Ghana and other developing countries, and has made recommendations to overcome them. The findings contribute to the existing literature on HTA especially in developing countries and the findings suggest new avenues for future research. The thesis concludes that HTA can be conducted and used for decision-making in the Ghanaian health system when measures are put in place to address the challenges reported in this thesis. However, in the short to medium term, the study recommends that HTA appraisals conducted in Ghana be restricted to generic medicines and non-patented health technologies.

11 APPENDICES

11.1 Appendix 1: The Ghanaian health system (additional information)

This section provides additional information on the Ghanaian health system presented in Chapter 1, Section 1.5.

11.1.1 Composition of the NHIS benefit package and coverage

Table 11-1: Composition of the NHIS of Ghana

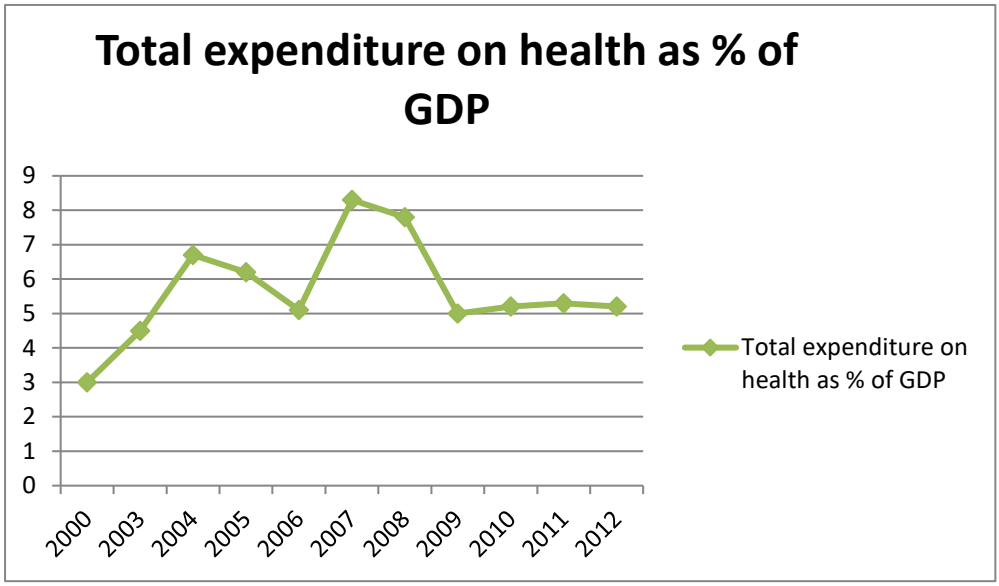
Who is covered	What services are covered	What proportion of health costs is covered
Exempt from payment of premium: • children below 18 years • pregnant women • persons with mental disorders • adults aged 70 years and above • indigents • formal sector employees Non-exempt from payment of premium: informal sector workers As at the end of 2014, only 38% of the population was covered by the NHIS. Formal sector workers are those who are employed by institutions and are paid on monthly basis, whereas informal sector workers are not. They rather may have their own businesses.	Benefit packages are mostly treatment interventions and includes: • general outpatient and inpatient care • eye care • comprehensive delivery care • oral health • emergency care • diagnostic tests • generic medications Other interventions are provided under government vertical programs. e.g. antiretroviral drugs for treatment of HIV/AIDS, and immunisation.	The scheme is funded through tax, social security deductions, grants and donations, parliamentary allocations, premium contributions from informal sector workers and registration fees from all enrolled persons. All treatment costs (according to agreed protocols) of conditions covered under the NHIS are fully covered including medicines for those conditions that are included in the NHIS medicine list. Enrolled clients may pay OOP for transportation, medicines that are not covered under the NHIS and for drugs that are not available at health facilities but are covered under the NHIS.

Source: NHIS 2013, Irene Agyepong et al., 2014, Witter and Garshong, 2009
*Coverage is not automatic for the exempt. One needs to register through a token payment (GHC5) to be covered.

11.1.2 Resources available for use in the health system

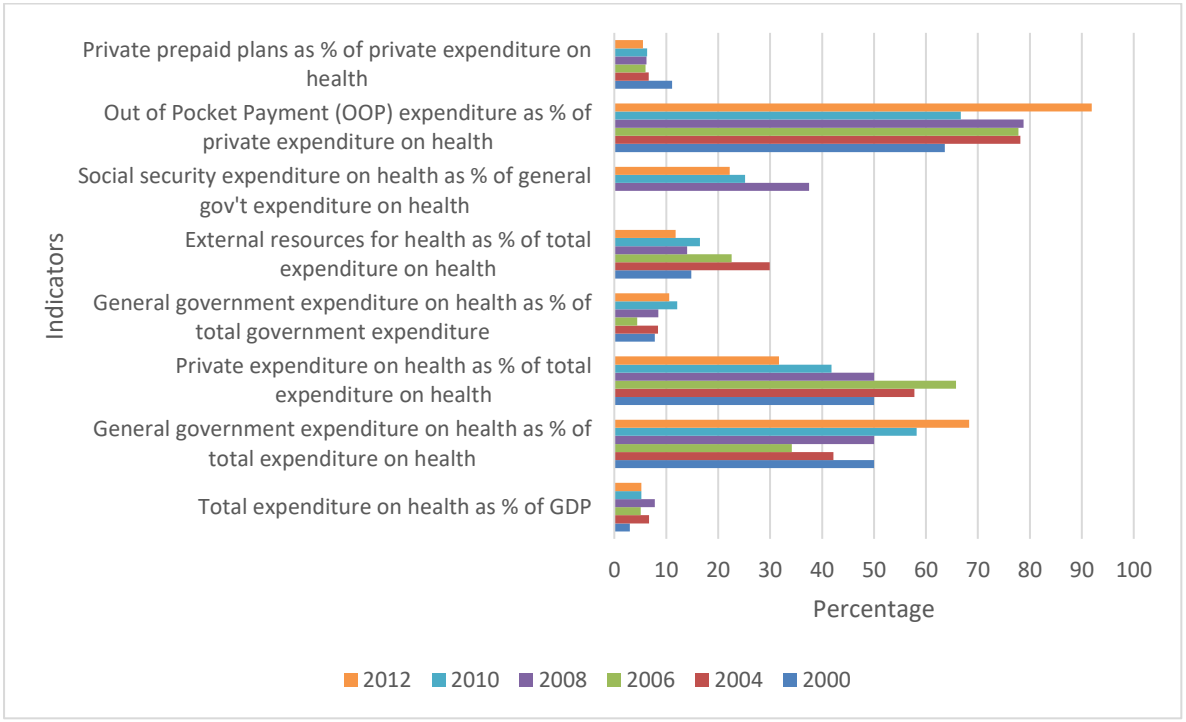
This study used health expenditure trends of the country as a proxy for resources available for spending in the health system. It was assumed that GDP of the country will directly affect the

percentage spent on health. Figure 11-1 demonstrates the total expenditure on health as a percentage of GDP of Ghana from year 2000 to 2012. The other indicators of the health spending trend of Ghana are shown in Figure 11-2.



Source: World Health Statistics 2015

Figure 11-1: Total Expenditure on health as a percentage of GDP in Ghana



Source: World Health Statistics reports 2006-15

Figure 11-2: Health Expenditure/Spending Trends

11.1.3 Service delivery in the Ghanaian health system - Composition and levels

There is a Public Private Partnership in the delivery of health care in Ghana. Both the government (public) and private entities deliver health care. The government facilities include, but are not limited to three teaching hospitals, three psychiatric hospitals, nine regional hospitals, district hospitals, polyclinics, health centres and CHPS compounds (319). In addition to the formal health care system, there is also the traditional system of delivering health services.

Table 11-2 describes the three-tier system of health care services, the levels of care, services provided under each and the category of health personnel who provide services at each level. Polyclinics, private hospitals, health centres and clinics, maternity homes and CHPS are the facilities that render primary health care to the populace. Regional (synonymous to state territories) and district hospitals (smaller hospitals with up to 100 bed capacity and synonymous with sub-regional hospitals) are the referral points for the primary care services, whereas the teaching hospitals are referral points for secondary care services. However, some referrals from primary care service providers go straight to the tertiary care provider depending on the proximity of health facility and the type of care need. The teaching hospitals and psychiatric hospitals, which are the main tertiary care providers, are the last point of referral.

Table 11-2: Organisation of services in Ghana

System of Care	Level of Organisation	Types of Health Facility	Type of Services Provided	Services Provided by Whom
Primary care services (Primary Health Care)	Community Sub-district	- Health centres or post - Community Based Health Planning and Services (CHPS) - Clinics - Maternity homes - Polyclinics	Primary health care services including both curative, promotive and preventive health services	Community Health Nurses Enrolled Nurses Midwives Community volunteers* Medical Assistants Physician Assistants Physicians**

System of Care	Level of Organisation	Types of Health Facility	Type of Services Provided	Services Provided by Whom
Secondary Care Services	District Regional	- District hospitals - Regional hospitals	- Primary health care services - Referrals from primary care services system - Surgeries - Other Specialist services	General Physicians Specialists Medical Assistants Physician Assistants Registered Nurses Community Health Nurses*** Enrolled Nurses***
Tertiary Care Services	National	-Teaching hospitals - Psychiatric hospitals	- Specialised Care - Academic training - Referrals from Primary and Secondary Care services system	General Physicians Specialists

*Works under the supervision of Community Health Nurses and Enrolled Nurses
**Polyclinics located in the cities
*** District hospitals that are located in rural areas

11.1.4 Formula used in allocating resources at the national level

Table 11-3: Formula for allocating resources

Levels	Factors Used for Funding Allocation
Office of Regional Director	40% shared equally between regions 30% according to number of districts 20% according to size of region (in km square) 10% according to distance of region from national capital
Regional Health Administrator	40% shared equally between regions 30% according to number of districts 20% according to size of region (in km square) 10% according to distance of region from national capital
Regional Public Health Units	50% evenly distributed 25% according to infant mortality rate 25% according to population
Regional Clinical Care Units	40% evenly distributed 60% according to size of region
Training Institutions	30% evenly distributed 70% according to student population
Regional Hospitals	30% evenly distributed 70% according to number of beds
District Health Administrations	30% evenly distributed 70% according to number of facilities
District Hospitals	30% evenly distributed 70% according to number of beds
Sub-districts	100% according to population of region

Source: Ensor et al. 2001

11.1.5 Selection of benefits package under the NHIS

11.1.5.1 Selection and pricing of NHIS Medicines List (NHIS ML)

The NHIS medicines list is derived from a process that involves the evaluation of evidence for the management of the common health problems seen in health facilities in Ghana, and the subsequent selection of appropriate medicines for their treatment (58). An ad hoc committee consisting of medical doctors, pharmacist and a midwife does the evaluation process. A technical group consisting of pharmacists, a doctor and a public health specialist undertakes pricing of selected drugs. The final list of medicines and their respective prices are arrived at after discussions with stakeholders (58). Medicines selected include all the Ghana Essential Medicines List (EML) and cover most of the common drugs prescribed for the management of conditions under the NHIS benefit package. A medicine should also have been authorised for use in the market by the FDA before it is listed on the NHIS ML. The most recent revised NHIS medicines list contains 517 formulations (58), and their respective unit of pricing and reimbursement prices as well as the levels of prescribing (that is facilities under which each drug can be prescribed). Levels of prescribing are adopted from the EML 2010 edition whose goal is to improve quality of care, promote the rational use of medicines and contain the escalating costs of medicines to the scheme (58, 59).

Medicines that are used for vertical programs (programs funded by donor agencies and non-governmental organisations and organised separately from the MOH program of work) such as vaccines for childhood immunisations and medicines for tuberculosis, and mental health care (with the exception of those used in general practice) are exempted from the list. This is because they are financed separately and some provided free of charge. Also exempted from the list are medical devices and supplies, and anaesthetic agents which are all captured under the tariffs for the diagnostic related groupings of services (i.e. the G-DRG) under the NHIS benefit package (52).

The prices of medicines on the NHIS medicine list is determined by a survey of medicines prices using the methodology of the World Health Organisation and Health Action International; the median prices of selected drugs are based on these. Manufacturers, wholesale distributors, private pharmacies, government, mission and private health facilities located in all ten regions of the country supply data on prices of generic drugs. For medicines that are still under patent protection, the innovator (brand) price is used in pricing. Prices of medicines reimbursed under the NHIS ranges from 0.05 Ghana Cedis (AUD 0.02) to 320 Ghana Cedis (AUD 116) per unit (58).

11.1.5.2 Selection and pricing of healthcare services under the NHIS

The minimum healthcare benefits and exclusion list for reimbursement under the NHIS are stipulated in the National Health Insurance Regulation LI 1809, 2004, Schedule (II) Part 1 (Regulation 19 (1)) and Part 2 (Regulation 20) respectively. However, the first committee that was commissioned to develop tariffs for health services and diseases given under the NHIS saw the need to select health services for reimbursement since some of the items captured by the LI 1809 Schedule II Part II were general and broad. They also left room for use of the NHIS funds by including all conditions not captured under the exclusion list. Selection of these health services was based on the epidemiology of diseases in Ghana (commonly treated diseases in Ghana that are characteristic of the country are those recorded to be seen frequently among out-patients. They include malaria, acute respiratory diseases, diarrhoeal diseases and hypertension), common procedures and operations that occur in Ghana and experiences of the committee members, all in accordance with the LI 1809 Schedule II Part II.

NHIS pays providers for all conditions and services listed on the benefit package. Tariffs designed for reimbursement of health care services do not include the costs of drugs (direct, indirect and overhead costs of pharmacy); and other costs related to drugs. It however includes the direct costs of providing services such as diagnostic investigations, consumables (such as

gloves, syringes, and adhesive plaster), anaesthesia and intensive care (for surgeries) (50). Tariffs/pricing was developed for groups of diagnosis with similar clinical treatments (using the International Classification of Diseases (ICD)-10) and was given the term Ghana Diagnostic Related Groupings (G-DRG). Currently, Ghana has a total of 611 inpatient and outpatient DRGs across 11 major diagnostic categories for which the NHIS reimburses.

The current tariff for each G-DRG was derived from the direct costs and indirect costs (including wages, utilities, capital equipment and maintenance, administration and housekeeping) associated with delivering those services and obtained from self-reporting of providers. Meanwhile, the government already pays salaries of health personnel employed by public and some mission-based health facilities and allocates some funding for administration of public hospitals, which results in some overlapping/doubling up of payments made to public health institutions by the government under the NHIS. Prices used for costing the tariff for the G-DRGs were derived from a survey conducted in 27 health facilities. The consultants who developed the current tariffs for the G-DRG claim to have estimated the cost implications of the tariffs on the overall NHIS budget using past claims frequencies for different providers. Like the pricing of the NHIS medicines list, stakeholders including health care providers are involved in the pricing of G-DRGs.

11.1.5.3 The Essential Medicines List

Essential medicines are medicines that satisfy the priority health needs of the population of Ghana. Their selection is with regard to public health relevance, evidence on efficacy, safety and comparative cost effectiveness. The last edition, which was also the sixth edition, was derived from the Standard Treatment Guideline (STG) of Ghana to ensure congruence in treatment, procurement and reimbursement. As such, all drugs in the STG are included in the EML. Some previous editions were produced using these same principles. In addition to this, drugs were also selected based on WHO criteria by an expert panel. The expert panel is an ad

hoc committee created for this purpose and consists of clinicians, pharmacists and a midwife. The criteria used for selection of drugs by the panel are that:

1. drug selection should be based on the results of efficacy and safety evaluations obtained in controlled clinical trials and epidemiological studies, and on the performance in general use in a variety of medical settings;
2. when several drugs are available for the same indication, only the drug and the pharmaceutical form that provides the more convenient benefit/risk ratio should be selected;
3. when two or more drugs are therapeutically equivalent, the selection should favour:
    - the drug that has been thoroughly investigated,
    - the drug with the most favourable pharmacokinetic properties,
    - the drug with the lowest cost, calculated on the basis of the whole course of treatment,
    - the drugs with which health workers are already familiar,
    - the drug for which economically convenient manufacturing is available in the country,
    - the drug which shows better stability at the available storage conditions.

The EML by law under the NDP is to be revised every two years. This is however not done. The first EML was compiled in 1988, followed by revisions in1993, 2000, 2004, and 2010. The most recent revision of the EML (now to be called National Medicines List) and the STG commenced in February 2015, but has not been completed to date. There are indications beside each drug of the EML on insurance coverage status. In all, the current EML lists 334 medicines (59).

11.2 Appendix 2: Data collection methods and instruments

11.2.1 Document 1: Consent form and Information Sheet – quantitative survey

Consent form

Participant statement and signature

I certify that I voluntarily agree to participate in this study by answering the questions in the interview. I have read the information given above and have been given the chance to ask questions concerning the study, all of which have been satisfactorily answered. I understand I am not obliged to participate in this study, hence I am free to discontinue participation at any time if I so choose.

Signature of interviewee Date

Investigator statement and signature

I certify that the participant has been given ample time to read and learn about the study. All questions and clarifications raised by the participant have been addressed. The participant has been informed of his voluntary participation and right to discontinue participation at any time if he/she so chooses. The participant has fully agreed to participate in the study.

Signature of Researcher or delegate Date

Information sheet

Project Title: The Feasibility of Health Technology Assessment (HTA) in the Ghanaian health system: Assessing the knowledge and attitudes of decision makers and researchers towards HTA in Ghana.

Introduction of self

My name is Rebecca Addo, a Ghanaian and currently a Ph.D student with the CHERE, at the University of Technology Sydney, Australia. The name of my Principal supervisor is Prof. Jane Hall, University of Technology Sydney, Australia, CHERE, P. O. Box 123 Broadway NSW 2007. She can be contacted by email through Jane.Hall@chere.uts.edu.au. The person overseeing this survey in Ghana is Justice Nonvignon (Ph.D), a lecturer at the University of Ghana, Legon, P. O. Box LG 13. He can also be contacted on phone through +233249832313.

Nature of Research/Background

This study is part of a thesis project that seeks to explore the feasibility of using health technology assessment (HTA) to inform health decision-making in Ghana, especially in the area of reimbursement of drugs on the National Health Insurance Scheme (NHIS) Medicine List. This initial survey is to investigate the perception of health decision makers and researchers/academics on the context in which decisions are made in the Ghana health system and explore their knowledge on economic evaluation. Results from the study would be useful in the development of a policy process that uses HTA and designing and setting up of the HTA agency as stated in The Health Act 2015.

What is involved/Procedures

A questionnaire will be administered face-to-face in your office. It will be left with you to give you ample time to complete the questionnaire so it does not interfere with your scheduled activities. Answering the questionnaire will take between 15 – 20 minutes of your time. You are been asked to partake in this study because of the role you play in the Ghanaian health sector. Your opinion and knowledge is very important and highly recognised as valuable to this study by the researcher. It will involve answering close ended questions on your perception of the current decision-making process in the Ghana health system, some of which involve rating and ranking. This interview does not seek to assess you, but rather seeks to understand your

opinion on the current decision-making process and what you think should be considered in such processes. Participation is voluntary, however it will be appreciated if you could participate in this study. Completed questionnaire will be coded and responses analysed as aggregates which cannot be traced back you in any way. This is purely an academic research which forms part of research student's work for the award of a Doctorate in Health Economics.

Potential Risks and Benefits

This study will not pose any risk in the form of bodily injury but might cause some inconvenience given that participant will have to spend 15-20 minutes of their time in answering the questionnaire. However, participants are given ample time to complete the questionnaire within his/her own scheduled time. On the other hand, both the study population and the society stand to benefit from this study. The findings of the study will be useful in planning the introduction of HTA into the decision-making process should it be adopted. Results of this study can be used to set the agenda for creating awareness on other efficient way of allocating health resources that is evidenced based such as HTA. It will also identify the factors that decision makers deem important for consideration in the decision-making process in the Ghana health system. This will be useful in planning and designing any new decision-making processes in the country.

Voluntary participation/Right to refuse

Written consent will be sought from study participants. Participation is not compulsory but purely voluntary; hence you have the right to stop answering the questionnaire and drop out of the study any time you want to without any penalty or adverse impacts in terms of the participant's employment.

Compensation/Payment

As a participant, you will not be compensated in money or in kind for taking part in this study.

Anonymity and confidentiality

Completed questionnaires will be coded and will not record the name of the study participant or the facility from which data was collected. It will be kept under lock and key and with a password accessible by only the research student, principal investigator and co-investigators. Information about you will be protected to the best of my ability. You will not be named in any reports. This will be done to ensure confidentiality of information collected from you as a participant. Electronic data will also be stored on the UTS cloud. Other electronic data will be stored on a CD-ROM and external hard drive as well which will all be kept under lock and key. All data collected will be kept by the research student for 8-10 years to allow for publication of the research, after which all data will be destroyed.

Outcome and Dissemination of Results

A presentation of initial findings will be presented to relevant stakeholders before final write-up is done. A summary of the findings of the study will be given to the government institutions who participated in the studies and all relevant stakeholders. Also, findings from the study will be published in a peer-reviewed journal and made available for participants and any other persons who find it useful. Findings of research will also be presented at international conferences where this topic area is discussed. In publications and conference presentations, participants and their institutions will be acknowledged. The research student will be the lead author, and supervisory panel, as well as anybody who actively participates in the design and writing of the paper, will be mentioned as contributing authors. This study will also form at least one chapter of a dissertation submitted by the research student for the award of a Doctor of Philosophy in Health Economics.

Source of funding

Self-financed

Contacts for additional information and clarification

In case of any questions or enquiries, Principal investigator, Prof. Jane Hall can be contacted through CHERE University of Technology, Sydney. P. O. Box 123 Broadway NSW 2007 or via email at Jane.Hall@chere.uts.edu.au. The research student, Miss Rebecca Addo, can be contacted through same address or by phone on + or through Rebecca.Addo@chere.uts.edu.au. Also, the person in Ghana who is overseeing this study, Dr. Justice Nonvignon can be contacted by mail via University of Ghana Legon, P. O. Box LG 13, Legon, Ghana. He can be also be contacted by phone on + or via email at jnonvignon@ug.edu.gh. The Ghana Health Service Ethics Committee administrator can be contacted through + for further clarification if need be.

11.2.2 Document 2: Questionnaire – quantitative survey

Project Title: The Feasibility of Health Technology Assessment (HTA) in the Ghanaian health system: Assessing the knowledge and attitudes of decision makers and researchers towards HTA in Ghana.

Introduction of self

Thank you for agreeing to participate in this study and to be interviewed. My name is Rebecca Addo, a PhD student from the University of Technology Sydney. This study is part of a thesis project that seeks to assess how feasible a low income country like Ghana which is constrained with data and human resource capacity among other challenges can establish and use HTA to inform health decisions. The current survey seeks to identify the perception of decision makers in health and academics/researchers on the current process of decision-making in the Ghana health system. I can be contacted through University of Technology Sydney, Australia,

CHERE, P. O. Box 123 Broadway NSW 2007 or via email by Rebecca.Addo@chere.uts.edu.au.

Background to the study

Decision-making about healthcare and health resource allocations in most developing countries is not transparent and is reported to be influenced by a number of factors including historical experiences and political factors. There is no documented literature on the knowledge of users on how health decisions are made at the national and local levels in Ghana. The current draft Health Bill 2015 mandates the establishment of an HTA agency and the use of HTA to make health care decisions in Ghana. Meanwhile, local context has to be factored in the design of any new process of making decisions. This study is part of a thesis project that seeks to explore the feasibility of using health technology assessment (HTA) to inform health decision-making in Ghana (for example, in the area of reimbursement of drugs on the National Health Insurance Scheme (NHIS) Medicine List). This initial survey is to investigate the context in which decisions are made in the Ghanaian health system. It seeks to assess the perception of stakeholders/ health workers on the current process of decision-making in the Ghanaian health system. Results from this study together with the findings of the entire thesis will be useful in the development of a policy process that uses HTA and in designing and establishing an HTA agency as stated in The Health Act 2015.

Decision-making is defined in this context as the processes taken by policy makers and health facility managers to make decisions concerning:

- ***Formulation of the Standard Treatment Guideline***
- ***Selection of the Essential Medicines List***
- ***Selection of the National Health Insurance Scheme (NHIS) medicines list***
- ***Selection of healthcare services to be covered under the NHIS***
- ***Distribution of centrally allocated resources***
- ***Procurement and allocation of medical equipment and devices***
- ***Reimbursement (payment) of the NHIS benefit package***

You have been asked to partake in this survey because of your current role in the Ghana health system. Your responses cannot be traced back to you. All responses will be treated as confidential. Analysis of the responses will also be done in aggregates and will not be linked to you in any way.

Section A: Demographic Information

Select the correct option by ticking (√) the box that corresponds to it.

1. Sex
   a. Male □
   b. Female □
2. What is the highest degree you have obtained?
   a. Diploma □
   b. Advanced Diploma □
   c. First degree □
   d. Masters □
   e. Ph.D □
3. What is your primary discipline?
   a. Medicine □
   b. Pharmacy □
   c. Physician Assistant□
   d. Nursing □
   e. Administration □
   f. Management □
   g. Public health □
   h. Other (specify).....
4. How many years have you been working in the health sector? (Years of experience)
   a. Less than 1 year □
   b. 1 to 5 years □
   c. 6 to 10 years □

d. More than 10 years □

5. What is your place of work?
   a. Clinical health facility □
   b. National public agency (e.g. at the Ministry of Health, NHIS) □
   c. Local public agency (e.g. regional health directorate, district health directorate) □
   d. Academia/research centre □
   e. Other (specify) □.....
6. What is your current position at your work place?
   a. Nurse □
   b. Pharmacist □
   c. Physician □
   d. Researcher □
   e. Anaesthetist □
   f. Physician Assistant □
   g. Policy maker □
   h. Manager □
   i. Other (specify) □.....

Section B: Perception on the current process of decision-making in the Ghana health system

7. Please consider the following statements and indicate **(using a tick (√))** how accurate these are **(in your opinion)** in relation to the current process of decision-making in the Ghana health system

	Strongly Disagree	**Disagree**	**Neither Agree/ Disagree/Uncertain**	**Agree**	**Strongly Agree**
I am aware of the current process of decision-making in the Ghana health system					
All the relevant stakeholders are involved in the current process of decision-making in Ghana					

	Strongly Disagree	Disagree	Neither Agree/ Disagree/Uncertain	Agree	Strongly Agree
The current process of decision-making in the Ghana health system is all inclusive					
The current process of decision-making in the Ghana health system is appropriate					
The current process of decision-making in the Ghana health system is fair					
The current process of decision-making in the Ghana health system is transparent					
My opinion is influential in the current process of decision-making in the Ghana health system					
The current process of decision-making in the Ghana health system is evidence-based					
The current process of decision-making in the Ghana health system ensures the appropriate use of public money					
The current process of decision-making in the Ghana health system ensures that every Ghanaian can have input into the decisions that are made					

8. Please **rank (number)** the following from 1 to 10 (**1= most important and 10 = least important)** in order of importance the factors **(in your opinion)** that influence decision makers in the current decision-making process in the Ghana health system.

Influencing factor	Rank
Disease burden (severity of disease)	
Geographical area	
Population group to benefit	
Diseases of the poor	
Equity	
Cost of the equipment, drug, treatment	
Evidence of safety of the equipment, drug, treatment	
Evidence of effectiveness of equipment, drug, treatment	
Evidence of cost effectiveness (i.e. the cost per quality life year gained)	
Impact on budget	

9. Please **rank (number)** the following stakeholders from 1 to 10 (**1= most influence and 10 = least influence)** according to those who have the most influence **(in your opinion)** on the current process of decision-making in the Ghana health system.

Stakeholder	**Rank**
Nurses	
Health managers/administrators	
Expert groups (e.g. committees formed to do make decisions)	
Physicians	
Pharmacist	
Politicians	
Consumer/patient groups	
Heads of government agencies and health facilities	
Health economist	
Academics/researchers	

10. Please **rank (number)** the following from 1 to 10 (**1= most important and 10 = least important)** in order of importance the factors that you think should be considered when making health decisions in the Ghana health system.

Factors to consider in decision-making	**Rank**
Disease burden (severity of disease)	
Geographical area	
Population group to benefit	
Diseases of the poor	
Equity	
Cost of the equipment, drug, treatment	
Evidence of safety of the equipment, drug, treatment	
Evidence of effectiveness of equipment, drug, treatment	
Evidence of cost effectiveness (i.e. the cost per quality life year gained)	
Impact on budget	

11. Please **rank (number)** the following stakeholders from 1 to 10 (**1= most influence and 10 = least influence)** in order of which stakeholder you think should have the most influence hence should be involved in decision-making process in the Ghana health system.

Stakeholder	**Rank**
Nurses	
Health managers/administrators	
Expert groups (e.g. committees formed to make decisions)	
Physicians	
Pharmacist	
Politicians	
Consumer/patient groups	
Heads of government agencies and health facilities	
Health economists	
Academics/researchers	

12. Do you have any knowledge or training in economic evaluation? **(Tick the (√) correct option)**

    a. Yes ☐

    b. No ☐

11.2.3 Document 3: Consent forms and information sheets – qualitative interviews

Consent form

Participant statement and signature

I certify that I voluntarily agree to participate in this study by answering the questions in the interview. I have read the information given above and have been given the chance to ask questions concerning the study, all of which have been satisfactorily answered. I understand I am not obliged to participate in this study, hence I am free to discontinue participation at any time if I so choose.

Signature of interviewee Date

Permission to record interview (Please tick the box if you agree to be recorded)

I agree that this interview be recorded by the interviewer as I have been assured of confidentially. ☐

Investigator statement and signature

I certify that the participant has been given ample time to read and learn about the study. All questions and clarifications raised by the participant have been addressed. The participant has been informed of his voluntary participation and right to discontinue participation at any time if he/she so chooses. The participant has fully agreed to participate in the study.

Signature of interviewer Date

Information sheet

Project Title: The Feasibility of Health Technology Assessment (HTA) in the Ghanaian health system: Assessing the knowledge and attitudes of decision makers and Researchers towards HTA in Ghana.

Introduction of self

My name is Rebecca Addo, a Ghanaian and currently a PhD student with the CHERE, at the University of Technology Sydney, Australia. The name of my Principal supervisor is Prof Jane Hall, University of Technology Sydney, Australia, CHERE, P. O. Box 123 Broadway NSW 2007. She can be contacted by email through Jane.Hall@chere.uts.edu.au. The person overseeing this survey in Ghana is Justice Nonvignon (PhD), a lecturer at the University of Ghana, Legon, P. O. Box LG 13. He can be contacted on phone through +233249832313.

Nature of Research/Background

This study is part of a thesis project that seeks to explore the feasibility of using health technology assessment (HTA) to inform health decision-making in Ghana, especially in the area of reimbursement of drugs on the National Health Insurance Scheme (NHIS) Medicine List. This initial survey is to investigate the context in which decisions are made in the Ghana health system and explore decision makers' knowledge on HTA, anticipated barriers to using it as well as ways of overcoming identified barriers. Results from the study would be useful in the development of a policy process that uses HTA and designing and setting up of the HTA agency as stated in The Health Act 2015.

What is involved/Procedures

An interview will be conducted in your office or any place you select as an interviewee to be convenient in your institution. The interview will take between 45-60 minutes of participants' time. You have been asked to partake in this study because of your active participation and experience in decision-making in the Ghanaian health sector. Your knowledge in this area is very important and highly recognised as valuable to this study by the researcher. It will involve

answering questions from an open-ended interview guide about the current practices used in allocating health resources and setting priorities, knowledge on health technology assessment, perceived barriers to its use as well as recommendations on how to address these barriers. This interview does not seek to assess you, but rather seeks to understand your knowledge in economic evaluation/HTA and how you perceive its applicability to the Ghanaian context. Participation is voluntary; however it would be appreciated if you could participate in this study. Responses of participants will be recorded with their consent and notes also taken. Only notes will be taken for participants who are not comfortable being recorded. Recordings will be transcribed and analysed together with notes taken as findings of the study. This is purely an academic research which forms part of research student's work for the award of a Doctorate in Health Economics.

Potential Risks and Benefits

This study will not pose any risk in the form of bodily injury but might cause some inconvenience given the length of the interview. It may be seen as examining your knowledge base in this area. However, participants are assured that the interview is an academic exercise that seeks to explore how you understand and interpret the concept of economic evaluation/HTA for decision-making. On the other hand, both the study population and the society stand to benefit from this study. The findings of the study will be useful in planning the introduction of HTA into the decision-making process should it be adopted. Results of this study can be used to set the agenda for creating awareness on other efficient way of allocating health resources that is evidenced based such as HTA. This can subsequently set the agenda for training in this area for potential users as well as the introduction of courses in health managers' programs. In addition to these benefits, other Sub-Saharan African countries can benefit from the results should they also decide to embark on using HTA as a decision-making criteria.

Voluntary participation/Right to refuse

A written consent and/or verbal consent will be sought from study participants. Participation is not compulsory but purely voluntary; hence you have the right to stop answering questions and the interview at any time, and drop out of study anytime you want to without any penalty or adverse impacts in terms of the participant's employment.

Compensation/Payment

As a participant, you will not be compensated in money or in kind for taking part in this study.

Anonymity and confidentiality

Notes taken from interview and responses transcribed will be coded and will not contain the name of the study participant or the facility from which data was collected. It will be kept under lock and key and with a password accessible by only research student, principal investigator and co-investigators. Information about you will be protected to the best of my ability. You will not be named in any reports. This will be done to ensure confidentiality of information collected from you as a participant. Electronic data will also be kept on the University of Technology Sydney (UTS) cloud. Other electronic data will be stored on a CD-ROM and external hard drive as well which will all be kept under lock and key. All data collected will be kept by the co- investigator for 8-10 years to allow for publication of the research, after which all data will be destroyed.

Outcome and Dissemination of Results

A presentation of initial findings will be presented to relevant stakeholders before final write-up is done. The findings of the study will be given to the government institutions who participated in the studies and to all relevant stakeholders. Also, findings from the study will be published in a peer-reviewed journal and made available for participants and any other persons who find it useful. Findings of research will also be presented at international conferences where this topic area is discussed. In publications and conference presentations,

participants and their institutions will be acknowledged. The research student will be the lead author, and supervisory panel, as well as anybody who actively participate in the design and writing of the paper, will be mentioned as contributing authors. This study will also form at least one chapter of a dissertation submitted by the research student for the award of a Doctor of Philosophy in Health Economics.

Source of funding

Self-financed

Contacts for Additional Information and Clarification

In case of any questions or enquiries, Principal investigator, Prof. Jane Hall can be contacted through CHERE University of Technology, Sydney. P. O. Box 123 Broadway NSW 2007 or via email at Jane.Hall@chere.uts.edu.au. The research student, Miss Rebecca Addo can be contacted through same address or by phone on + or through Rebecca.Addo@chere.uts.edu.au. Also, the person in Ghana who is overseeing this study; Dr. Justice Nonvignon can be contacted by mail via University of Ghana Legon, P. O. Box LG 13, Legon, Ghana. He can be also be contacted by phone on + or via email at jnonvignon@ug.edu.gh. The Ghana Health Service Ethics Committee administrator can be contacted through + for further clarification if need be.

11.2.4 Document 4: Summary of subject area for interviewees

Health Technology Assessment

Health technology is an intervention that may be used to promote health, to prevent, diagnose or treat acute or chronic disease, or for rehabilitation. It includes pharmaceuticals, devices, procedures and organisational systems used in health care.

Health technology assessment is the systematic evaluation of the properties and effects of a health technology to ascertain its direct/intended and indirect/unintended effects and

consequences to enable decision makers' make informed decisions on the its adoption and funding. It is used for allocation of resources, reimbursement decisions and formulation of the insurance benefit package and clinical guidelines to mention a few.

The methods and applications of HTA are broad. It includes budget impact analysis, economic evaluations, expert opinions, qualitative analysis, post-market surveillance, clinical trials and systematic reviews, with economic evaluation being widely used. In HTA, the efficacy, safety, effectiveness and cost effectiveness of the technology is assessed as well as its financial impact on the health system's budget. It provides estimates of how a new technology will impact the health spending on that condition the technology will be used for as well as the overall short-medium term annual budgets of decision makers both at the local and national level. It also reveals the overall impact of adoption of the new technology on service provision.

Economic evaluation

Economic evaluation is a comparative analysis of two or more alternative course of actions in terms of both their costs and consequences; thus providing a basis for resource allocation decisions that maximise societal welfare. It provides information about what intervention/ course of action represents the best use of scarce health resources and value for money. There are three main types of economic evaluation used in healthcare delivery for allocation of resources; cost minimisation analysis, cost effectiveness analysis and cost utility analysis.

The differences between them are summarised in the table below:

Differences in the three types of economic evaluations commonly used in HTA

Cost minimisation analysis	Cost effectiveness analysis	Cost utility analysis
Compares two options with the same outcome to determine the one that is the cheapest	Compares two options or interventions with different outcomes	Compares two or more alternatives with different outcomes

The objective is to minimise cost	The objective is to compare the costs and effectiveness of one or more alternatives/options	The objective is to compare costs between alternatives
Cannot be used for options with different outcomes	Can be used for two or more alternatives with different outcomes	Can be used to compare two or more alternatives with different outcomes
Does not measure effectiveness of options under analysis	Measures the effectiveness and efficacy of alternatives	Outcome of alternatives under analysis differ in efficacy
	Outcome measure is measured in natural units, e.g. deaths averted	Outcome measure is measured in common metric called Quality Adjusted Life Years. This allows for comparability across different diseases and treatments

11.2.5 Document 5: Interview guide

Interview Guide for Decision makers

Introduction of self

Thank you for agreeing to participate in this study and to be interviewed. My name is Rebecca Addo, a PhD student from the University of Technology Sydney. My research is about assessing the perception of decision makers' about the use of Health Technology Assessment as a criterion for health decision-making in Ghana. This survey is part of my Doctoral dissertation which is looking at the feasibility of using health technology to inform health decision-making in Ghana. As you might have read from the initial summary of the subject area under discussion, health technology is an intervention that may be used to promote health, to prevent, diagnose or treat acute or chronic disease, or for rehabilitation. It includes pharmaceuticals, devices, procedures and organisational systems used in health care. Health technology assessment is the systematic evaluation of the properties and effects of a health technology to ascertain its direct/intended and indirect/unintended effects and consequences to enable decision makers' make informed decisions on its adoption and funding. It is used for

allocation of resources, reimbursement decisions and formulation of clinical guidelines to mention a few. Resource allocation is how resources are distributed among competing needs, facilities and geographical areas.

Current practices/criterion used in making decisions and challenges of the system

1. What is your current position?
2. Could you please tell me about your role/Job description or content

Could you please tell me the role you play in decision-making concerning:

- Allocating resources to the different areas under the health system, various regions (MOH and GHS representative)
- Allocating health resources to the various districts (regional health directors)
- Allocating resources to the facilities under your districts (district health directors)
- Inclusion and exclusion of drugs on the Ghana essential medicines list (GNDP representative)
- Selection of medicines and medical interventions for reimbursement under the NHIS (NHIS representative)

3. What process do you use for making decisions?

Could you please enlighten me on the process you take in carrying out such roles? For example, is there a laid down guideline, protocol or formula that you use for this exercise? Is there a committee that does this?

4. What factors are considered in making decisions?

What factors do you consider apart from the outlined process in making these decisions?

5. How are decisions on rationing of resources made? What factors are considered?

In instances where resources are scarce, and you need to allocate them to your district for example, how do you ration/share such resources among your coverage area? What factors do you consider?

6. What are some of the current challenges with the way in which you make decisions currently? (Prompt interviewee to mention the ones which are peculiar to their position)

7. Is there an explicit process of reviewing how decisions are made (prompt if answer is not forthcoming - like how the health system program of work is reviewed every year to measure its performance)? (Give examples of uses of cost effectiveness analysis, needs of the population)
8. Do have knowledge about current processes used in making the following decisions in Ghana? (State the listed decisions below one after another). If yes, tell me about it.

- Formulation of the standard treatment guideline
- Selection of the essential medicines list
- Selection of the National Health Insurance Scheme (NHIS) medicines list
- Selection of healthcare services to be covered under the NHIS
- Equipment procurement
- Reimbursement of the NHIS benefit package

Recommendations to improve the current practices/criterion used in making decisions

1. Suggest any criterion you deem appropriate for using to make such decisions?

Knowledge on Health Technology Assessment/Economic evaluation

1. Have you ever heard of Economic evaluation?
   If yes; where? Could you tell me your understanding of it and its uses?
   (If no, explain what it is. Explain what it is to those who said yes as well. Refer to demonstration card 1for definition of economic evaluation)
2. Have you heard of Health Technology Assessment?
   If yes; where? Tell me your understanding of it and its uses.
3. Do you know of any instance where economic evaluation studies or HTA was used to inform decision-making in Ghana?

Perceived anticipated barriers to the use of HTA

1. What do you perceive as some of the barriers to the introduction of HTA as a criterion for decision-making?

(Prompt questions: Ask about what they think of Ghana's current capacity in conducting HTA – does the existing work force have the skills required? Do we have enough people to conduct HTA?)

Perceived ways of addressing barriers and fostering the uptake of HTA

1. How can the barriers you just stated be overcome?
2. What other ways can the use of HTA as a criterion for decision-making be fostered in Ghana?

Interview Guide for Researchers

Introduction of self

Thank you for agreeing to participate in this study and to be interviewed. My name is Rebecca Addo, a PhD student from the University of Technology Sydney. My research is about assessing the perception of decision makers' about the use of Health Technology assessment as a criterion for health decision-making in Ghana. This survey is part of my Doctoral dissertation which is looking at the feasibility of using health technology to inform health decision-making in Ghana. As you might have read from the initial summary of the subject area under discussion, health technology is an intervention that may be used to promote health, to prevent, diagnose or treat acute or chronic disease, or for rehabilitation. It includes pharmaceuticals, devices, procedures and organisational systems used in health care. Health technology assessment is the systematic evaluation of the properties and effects of a health technology to ascertain its direct/intended and indirect/unintended effects and consequences to enable decision makers' make informed decisions on its adoption and funding. It is used for allocation of resources, reimbursement decisions and formulation of clinical guidelines to mention a few. Resource allocation is how resources are distributed among competing needs, facilities and geographical areas.

Knowledge on how current decisions are made in the health sector

1. What processes do you know/think are used by health decision makers in Ghana for decision-making?
2. What do you think are some of the factors that affect their decision-making?

3. How are decisions on rationing of resources made? What factors are considered?
4. What do you think are some of the challenges decision makers' face when making such decisions?
5. Is there an explicit process of reviewing how decisions are made in the Ghana health system? (prompt if answer is not forthcoming - like how the health system program of work is reviewed every year to measure its performance) (Give examples of uses of cost effectiveness analysis, needs of the population)
6. Do have knowledge about current processes used in making the following decisions in Ghana? (State the listed decisions below one after another). If yes, tell me about it.

- Formulation of the standard treatment guideline
- Selection of the essential medicines list
- Selection of the National Health Insurance Scheme (NHIS) medicines list
- Selection of healthcare services to be covered under the NHIS
- Equipment procurement
- Reimbursement of the NHIS benefit package

7. Suggest any criterion you deem appropriate for using to make such decisions?

Knowledge on Health technology assessment

1. Have you been involved in any study in economic evaluation before? (it is assumed that respondents purposively selected have prior knowledge in economic evaluation)
2. Why was it conducted? Was it an academic exercise or it was commissioned by the Ministry of Health?
3. What was the source of funding?
4. Were the findings from this study used for decision-making by health decision makers?
5. What do you think are some of the barriers to conducting such studies?
6. Have you ever heard of Health Technology Assessment?
7. If yes; where? Tell me your understanding of it and its uses.

Perceived anticipated barriers to the use of HTA

1. What do you perceive as some of the barriers to the introduction of HTA as a criterion for decision-making

(Prompt question: ask about what they think of Ghana's current capacity in conducting HTA – does the existing work force have the skills required? Do we have enough people to conduct HTA?)

Perceived ways of addressing barriers and fostering the uptake of HTA

2. How can the barriers you just stated be overcome?
3. What other ways can the use of HTA as a criterion for decision-making be fostered in Ghana?

11.3 Appendix 3: HTA in Ghana: Perception of clinical health workers about the current decision-making process

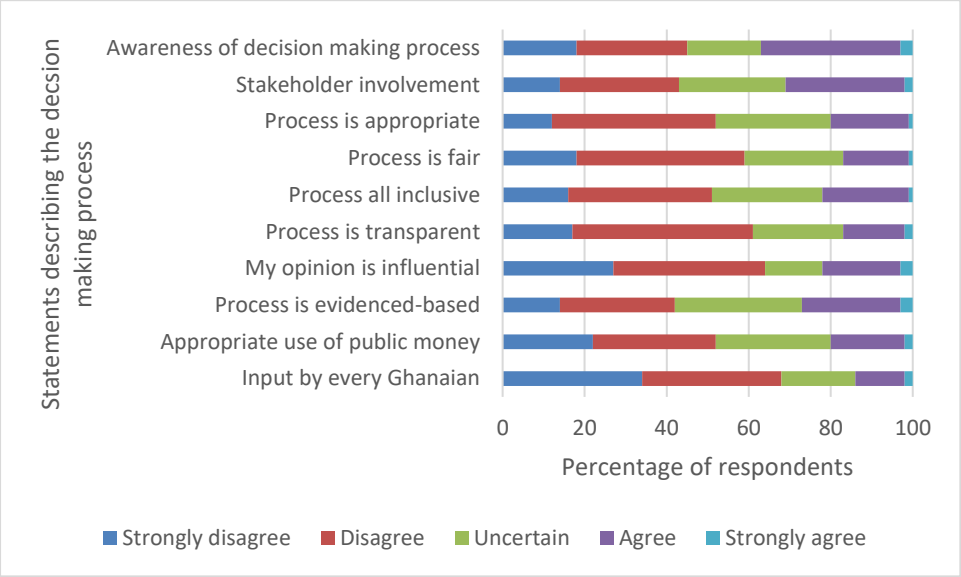


Figure 11-3: The perceptions of clinical decision makers about the current decision-making process in the Ghanaian health system

11.4 Appendix 4: HTA in Ghana: The current technical capacity

Table 11-4: Consolidated Health Economics Evaluation Reporting Standards (CHEERS)

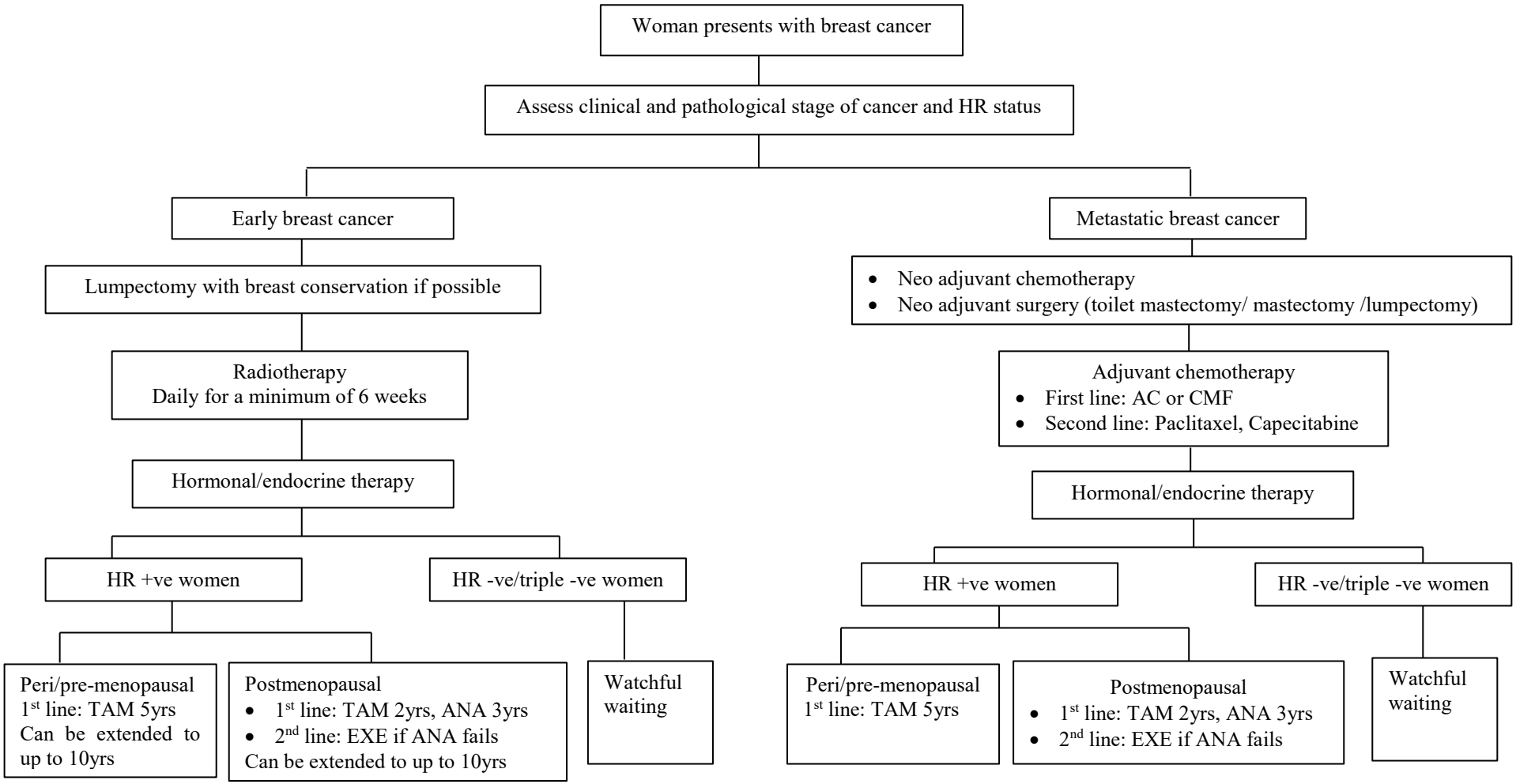
Section/item	Item number	Recommendations for reporting
Title and abstract		
Title	1	Identify the study as an economic evaluation or use more specific terms such as 'cost effectiveness analysis', and describe the interventions compared.
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.
Introduction		
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.
Methods		
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.
Measurement of effectiveness	11a	Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.
	11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.
Measurement and valuation of preference-based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.
Estimating resources and costs	13a	Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.

Section/item	Item number	Recommendations for reporting
	13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.
Analytic methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.
Results		
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost effectiveness ratios.
Characterising uncertainty	20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).
	20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.
Discussion		
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.
Other		
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.

Section/item	Item number	Recommendations for reporting
Conflict of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.

11.5 Appendix 5: HTA in Ghana: Justification for case study and identification of data

11.5.1 Clinical management algorithm for the treatment of breast cancer in Ghana



Abbreviations: +ve: positive, -ve: negative, ANA: anastrozole, AC: adriamycin and cyclophosphamide, CMF: cyclophosphamide, methotrexate and fluorouracil, EXE: exemestane, HR: hormone receptor, TAM: tamoxifen, yrs: years

Figure 11-4: Clinical management algorithm for the treatment of breast cancer in Ghana

11.5.2 Systematic review of economic evaluation studies on tamoxifen for the adjuvant treatment of breast cancer

Table 11-5: Summary of studies identified in the search for economic evaluation studies conducted on tamoxifen for breast cancer treatment

	Cochrane	EMBASE and Medline	PubMed	NICE	CADTH	PBAC	HITAP	CMeRC
Number of citations retrieved by search	117	1493	168	15	17	1	16	0
Number of citations excluded after title/abstract review								
Not an economic evaluation or systematic review of economic evaluation studies	54	1371	87	15	17	1	16	0
An economic evaluation or systematic review but not specific to tamoxifen	14	67	30	0	0	0	0	0
Intervention not tamoxifen for breast cancer	0	0	0	0	0	0	0	0
Population not women with breast cancer	0	0	0	0	0	0	0	0
Total number of citations excluded	68	1438	117	15	17	1	16	0
Number of citations eligible for full text screening	49	55	51	0	0	0	0	0
Consolidated number of citations included for full text screening after removing exact duplicates across different databases	75							
Number of citations excluded after full text screening								
Not an economic evaluation or systematic review of economic evaluation studies	3							
An economic evaluation or systematic review but not specific to tamoxifen	4							
Comparator not anastrozole or no treatment/watchful waiting/placebo	15							
Intervention not tamoxifen for treatment of breast cancer	6							
Systematic reviews and executive summaries	9							
Population not women with breast cancer	0							
No published data/conference presentation	18							
Total number of citations excluded	55							
Number of citations included for quantitative and qualitative synthesis	**20**							

Table 11-6: Summary of economic evaluations on tamoxifen identified in the literature – 1

Study	Perspective	Stage of cancer	Type of evaluation	Currency and year
Dranitsaris, Verma and Trudeau (2003)	Healthcare system	Advanced breast cancer	CUA	2003 Can$
Simons, Jones and Buzdar (2003)	Healthcare system	Advanced breast cancer	NR	2003 USD
Hillner (2004)	Health payer	Early breast cancer	CUA and CEA	USD (year not specified)
Gil et al. (2006)	Healthcare system	Early breast cancer	CUA and CEA	2004 Euros
Lonning (2006)	Healthcare system	Early breast cancer	CUA	2004 USD
Moeremans and Annemans (2006)	Healthcare system	Early breast cancer	CUA and CEA	Euros (year not specified)
Rocchi and Verma (2006)	Healthcare system	Early breast cancer	CUA and CEA	2004 Can$
Locker et al. (2007)	Healthcare system	Early breast cancer	CUA and CEA	2003-4 USD
Mansel et al. (2007)	Healthcare system	Early breast cancer	CUA and CEA	2003-4 £
Skedgel et al. (2007a)	Direct payer	Early breast cancer	CUA	2005 Can$
Skedgel et al. (2007b)	Healthcare payer	Early breast cancer	CUA	2005 Euros
Younis et al. (2007)	Third party payer	Early breast cancer	CUA	2005 Can$
Karnon, Delea and Barghout (2008)	Healthcare system	Early breast cancer	CUA and CEA	2005 £
Fonseca, Araujo and Saad (2009)	Private healthcare sector	Early breast cancer	CEA	2005 Brazilian Reais (R$)
Thomas et al. (2009)	Not specified	Not specified	CEA	£
Lee et al. (2010)	Societal	Early breast cancer	CUA	2009 Korean Won
Lux et al. (2010)	Public health insurance	Early breast cancer	CUA and CEA	2008 Euros
Yang et. al (2010)	Societal	Early and advanced breast cancer	CEA	2005-6 USD
Lux et al. (2011)	Healthcare system	Early breast cancer	CUA and CEA	2010 Euros
Shih et al. (2012)	Societal	Early breast cancer	CUA and CEA	2010 Singapore$

Table 11-7: Summary of economic evaluations on tamoxifen identified in the literature – 2

Study	Methods of synthesis	Time horizon	Cycle length	Discount rate	Base case results	
Dranitsaris, Verma and Trudeau (2003)	Decision tree	Start of first HT until disease progression	NA	Not reported	Cost[Can$]/ QAPFSB gained per year 19,600	
Simons, Jones and Buzdar (2003)	Not reported	Not reported	Not reported	Not reported	**Cost [US$]/QALY** • Indemnity: 9372 • PPO: 13,183 • POS: 11,893 • HMO: 8,921	
Hillner (2004)	Markov	4,8,12 and 20yrs	Not reported	3% for both costs and benefits	**Cost [US$]/LYS** • 4yrs: 1,112,000 • 8yrs: 35,400 • 12yrs: 96,000 • 20yrs: 40,600 •	**Cost [US$] /QALY** • 4yrs: 533,000 • 8yrs: 201,800 • 12yrs: 111,300 • 20yrs: 75,900
Gil et al. (2006)	Markov	10 and 20yrs	Not reported	3.5% for both costs and benefits	**Cost [€]/LYS** • 10yrs: 65,313 • 20yrs: 33,282	**Cost [€] /QALY** • 10yrs: 104,272 • 20yrs: 62,477
Lonning (2006)	Not reported	Not reported	Not reported	3% for both costs and benefits	**Cost [US$] /QALY (**N-/ N+(LQ of 0.9,0.8,0.7) • 55yrs: 35.294/ 33.43, 40.095/37.91, 46.279/43.763 • 65yrs: 46.991/44.43, 53.433/50.52, 61.922/58.555 75yrs: 74.585/70.52, 85.309/80.67, 99.759/94.334	
Moeremans and Annemans (2006)	Markov	20yrs	6 months	Not reported	**Cost [€]/LYS** • 4,233	**Cost [€]/QALY** • 4,495
Rocchi and Verma (2006)	Markov	Lifetime	One year	5% for both costs and benefits	**Cost [Can$]/LYS** • 3yr ATAC results- 29,043 • 5yr ATAC results- 30,137	**Cost [Can$] /QALY** • 3yr: 25,818 • 5yr: 27,877
Locker et al. (2007)	Markov	25yrs	3-month cycle for first 5yrs and 6month interval thereafter	3% for both costs and benefits	**Cost [US$]/LYS** • 23,541	**Cost [US$]/QALY** • 20,246

Study	Methods of synthesis	Time horizon	Cycle length	Discount rate	Base case results	
Mansel et al. (2007)	Markov	25yrs	3-month cycle for first 5yrs and 6month interval thereafter	3.5% for both costs and benefits	**Cost [£]/LYS** • 18,702	**Cost [£]/QALY** • 17,656
Skedgel et al. (2007a)	Markov	10 and 20yrs	Monthly	3% for both costs and benefits	**Cost [US$] /QALY** • 10yr: 67,017 • 20yr: 27,622	
Skedgel et al. (2007b)	Markov	20yrs	Monthly	3% for both costs and benefits	**Cost [€] /QALY** 19,982	
Younis et al. (2007)	Markov	10yrs (20 yrs in SA)	Monthly	3% for both costs and benefits	Not reported but mentioned it is cost effective within a US$50,000/QALY threshold	
Karnon, Delea and Barghout (2008)	Markov	50yrs	Annual	3.5% for both costs and benefits	**Cost [£]/LYS** • 11,703	**Cost [£]/QALY** • 11,428
Fonseca, Araujo and Saad (2009)	Markov	Lifetime	Not reported	3% for costs and 1.5% for benefits	**Cost [R$ (Brazilian $)]/LYS** 27,326.80 (US$10,930.72)	
Thomas et al. (2009)	Not reported	Not reported	NA	NR	**Cost [£]/LYS** • 5yr ANA: 17,244 • 2yr TAM, 3yr ANA: 11,173	
Lee et al. (2010)	Markov	35yrs	Not reported	5% for both costs and benefits	**Cost [Korean won]/ QALY** • All patients: 22,461,689 ($19,532.01) • Node –ve: 19,717,770 ($17,145.98) • Node +ve: 25,015,610 ($21,752.82)	
Lux et al. (2010)	Markov	25yrs	3-months cycle for first 5yrs and 6-months interval thereafter	3% for both costs and benefits	**Cost [€] /LYS** • 23,412	**Cost [€] /QALY** • 21,069
Yang et. al (2010)	A simple decision tree	20yrs	NA	0% in baseline analysis, but 5% and 10% used in SA	**Cost [US$] /LYS** EBC • ER+/PR+: 739 to 1939 • ER+ or PR+ (but not both): 1217 to 3107 • aged ≥50 = -462 to -3738 ABC cost effective regardless of HR status	
Lux et al. (2011)	Markov (hybrid)	20yrs	Not reported	3% for both costs and benefits	**Cost [€] /LYS** • 141,673.73	**Cost [€] /LYS** • 94,648.03

Study	Methods of synthesis	Time horizon	Cycle length	Discount rate	Base case results	
Shih et al. (2012)	Markov	Lifetime	One year	3% for both costs and benefits	**Cost [S$ (Singapore dollars)] /LYS** • 207,402	**Cost [S$ /QALY** • 114,061

Table 11-8: Key model inputs and their sources – systematic review of economic evaluation studies on tamoxifen

Study	Level of evidence of clinical data	Source of probabilities for recurrence/disease states	Efficacy estimates	Source of probabilities for adverse events	Utility weights	Source of utility weights
Dranitsaris, Verma and Trudeau (2003)	Meta-analysis (7 RCT)	Falkson and Falkson, 1996; Thurliman et al. 1996; Bonnetere et al.2000; Nabholtz et al. 2000; Moursidsen et al. 2001; Hayes et al. 1995	Tumour response rate, PFS	Same as source for disease states, plus seven comparative studies on the use of chemotherapy (refer to paper for details)	No response and progression during FAC:0.45 No response to anastrazole but response to FAC: 0.67 Response to anastrozole: 0.80	Dranitsaris et al. 2000 Estimated from 25 Canadian women living in Ontario
Simons, Jones and Buzdar (2003)	Trial (the North American trial)	The North American trial Nabholtz et al. 2000	PFS/TTP and clinical benefit (complete response plus stable dx for≥24wks	The North American trial Nabholtz et al. 2000	Time without AEs or disease progression: 1.00 Time with any toxicity: 0.50 In SA weights were varied according severity of toxicity as follows: Mild toxicity: 0.70 Moderate toxicity: 0.50 Severe toxicity: 0.30	Glasziou et al. 1998 Quality adjusted time without symptoms and toxicity method (Q-TWiST) method of quality adjustment. Time with any toxicity was given a weight of 0.5 but was varied according to severity of toxicity in a SA.

Study	Level of evidence of clinical data	Source of probabilities for recurrence/disease states	Efficacy estimates	Source of probabilities for adverse events	Utility weights	Source of utility weights
Hillner (2004)	Trial (ATAC)	ATAC trial Baum et al. 2003; and Baum et al. 2002	Event-free survival and overall survival	ATAC trial Baum et al. 2003; and Baum et al. 2002	Local breast recurrence: 15days CL breast cancer: 45days SR: 0.70 Hip fracture: 0.70 Vaginal bleeding: 15days VTE: 30days	Harvard school of public health. CEA registry 2004 Expert opinion
Gil et al. (2006)	Trial (ATAC)	The ATAC trialist group 2002	DFS	The ATAC trialist group 2002	DF without complications: 0.820 DF with complications: 0.741 LR: 0.718 Metastasis: 0.462 Death: 0.000	Gabriel et al. 1999; Brunner et al. 2005; Nicholson et al. 2001 and Karnon et al. 2002.
Lonning (2006)	Trial and EBCTCG meta-analysis data	Group EBCTCG 1998 Baum et al. 2002	RFS	ATAC trial Baum et al. 2002	Not reported	Dekonong et al. 1991, Norum et al. 1997 Derived from the general population
Moeremans and Annemans (2006)	Trial (ATAC) and other published data	Howell et al. 2005; Moran et al. 2002, Bonneterre et al. 2001 and Chang et al. 2003	Not reported	ATAC trial (Howell et al. 2005) and others; Moran et al. 2002, Bonneterre et al 2001 and Chang et al. 2003	DF first year: 0.86 DF consecutive years: 0.92 LR relapse: 0.51 Remission (follow-up): 0.81 Metastatic cancer: 0.54	Karnon et al. 2003
Rocchi and Verma (2006)	Trial (ATAC) and EBCTCG meta-analysis data	ATAC trialist group, 2005, 2003, 2002; EBCTCG 1998	DFS	ATAC trial group 2005, 2003, 2002; probabilities on the distribution of first events was confirmed by: Boccardo et al. 1992; Fisher et al. 1989; Fisher et al. 1997;	DF survival: 0.974 LR: 0.816 CL BC: 0.775 DR (was assigned from time of DR until death): 0.724	Benedict, Brown and Sorensen 2004

Study	Level of evidence of clinical data	Source of probabilities for recurrence/disease states	Efficacy estimates	Source of probabilities for adverse events	Utility weights	Source of utility weights
				Fisher et al. 1990; Pritchard et al. 1997; Rivkin et al. 1994		
Locker et al. (2007)	Trial (ATAC) and supported by other published literature	ATAC trialist group 2005; Kampy and Sengelov 1997; Moran and Haffty 2002; Stocker et al. 2000	DFS	ATAC trialist group 2005; Kampy and Sengelov 1997; Moran and Haffty 2002; Stocker et al. 2000	DF, no AEs: 0.965 Common AEs (tamoxifen): 0.956 Common AEs (anastrozole): 0.958 Vaginal bleeding: 0.926 Wrist fracture: 0.852 Local/regional recurrence: 0.766 HT for DR: 0.642 Endometrial cancer: 0.839 Spine fracture: 0.751 New CL BC: 0.702 DVT: 0.729 PE: 0.741 Hip fracture: 0.664 Chemotherapy for DR: 0.288 MI: 0.750 Stroke: 0.707 Hysterectomy: 0.899	Sorensen et al., 2004 (A cross-sectional studies of 44 women of mean age 67.5yrs with EBC); Tengs and Wallace 2000; Garry et al. 2004
Mansel et al. (2007)	Trial (ATAC) supported by and other published literature	ATAC trialist group 2005; Kampy and Sengelov 1997; Moran and Haffty 2002; Stocker et al. 2000	DFS	ATAC trialist group 2005; Kampy and Sengelov 1997; Moran and Haffty 2002; Stocker et al. 2000	DSF, no adverse events: 0.989 Common AEs (tamoxifen): 0.970 Common AEs (anastrozole): 0.962 Vaginal bleeding: 0.933 Endometrial cancer: 0.913 Wrist fracture: 0.916 New CL BC: 0.914 Local/regional recurrence: 0.911 DVT: 0.922 PE: 0.890 Spinal fracture: 0.894 Hip fracture: 0.858	Cross-sectional studies of 26 UK patients with mean age of 68yrs with EBC or ABC.

Study	Level of evidence of clinical data	Source of probabilities for recurrence/disease states	Efficacy estimates	Source of probabilities for adverse events	Utility weights	Source of utility weights
					HT for DR: 0.882 Chemotherapy for DR: 0.710 Current health: 0.933 Hysterectomy: 0.899	
Skedgel et al. (2007a)	Trial (ATAC), EBCTCG meta-analysis data and other CEA study	ATAC trialist group 2002, 2003, 2005; EBCTCG 1998; Hilner BE 2004;	DFS; but TTR in a SA	ATAC trialist group 2002, 2003, 2005; EBCTCG 1998; Hilner BE 2004;	DF: 1.00 First LC relapse: 0.70 Second LC relapse: 0.50 Well after LC: 0.96 Distant cancer relapse: 0.75 HT: 0.99 Vaginal bleeding: 0.50 Endometrial cancer (1st year): 0.58 Endometrial cancer (subsequent): 0.88 VTE: 0.64 Fractures (acute phase): 0.80 Fractures (chronic phase): 0.98	The CEA registry (2005) Tufts Medical Centre
Skedgel et al. (2007b)	Trial (ATAC), EBCTCG meta-analysis data and other CEA study	ATAC trialist group 2002, 2003, 2005; EBCTCG 1998; Hilner BE 2004;	DFS; but TTR in a SA	ATAC trialist group 2002, 2003, 2005; EBCTCG 1998; Hilner BE 2004	Well off treatment: 1.00 HT: 0.99 First LC relapse: 0.70 Second LC relapse: 0.50 Well after LC: 0.96 Distant cancer relapse: 0.75 Vaginal bleeding: 0.50 Endometrial cancer (1st year): 0.58 Endometrial cancer (subsequent): 0.88 VTE: 0.64 Fractures (acute phase): 0.80 Fractures (chronic phase): 0.98	The CEA registry (2005) Tufts Medical Centre
Younis et al. (2007)	Trial (ATAC), EBCTCG meta-analysis data	ATAC trialist group 2002, 2003, 2005; EBCTCG 1998;	DFS; but TTR in a SA	ATAC trialist group 2002, 2003, 2005; EBCTCG 1998;	Well on therapy: 0.99 Well off therapy: 1.00 Local relapse (first): 0.70 Local relapse (second): 0.50	The CEA registry (2005) Tufts Medical Centre

Study	Level of evidence of clinical data	Source of probabilities for recurrence/disease states	Efficacy estimates	Source of probabilities for adverse events	Utility weights	Source of utility weights
	and other literature	electronic medicines compendium 2005		electronic medicines compendium 2005	Local relapse (Treated): 0.90 Distant relapse: 0.60 Vaginal bleeding: 0.50 Endometrial cancer (1st year): 0.58 Endometrial cancer (after 1st year): 0.88 TE: 0.64 Fractures (1st year): 0.80 Fractures (after 1st year): 0.98	
Karnon, Delea and Barghout (2008)	EBCTCG meta-analysis data	EBCTCG 2005	DFS	EBCTCG 2005; BIG 1-98 2005; ATAC trialist group 2005; Karnon and Brown 2002; Moran and Hafty 2002; Haylock et. al. 2000; Schmoor et al. 2000; Kamby and Sengelov 1997; Borner et al. 1994; Toonkel et. al. 1983	DF: 0.989 CL tumour (Year 1): 0.911 CL tumour (Year 2+): 0.989 LRR (year 1): 0.911 LRR (year 2+): 0.989 Distant metastases: 0.796	Kanis et al. 2002 (26 UK postmenopausal women with EBC who have experienced adjuvant therapy); and Sorensen et al. 2004 (a cross-sectional studies of 44 women of mean age 67.5yrs with EBC)
Fonseca, Araujo and Saad (2009)	Trial (ATAC) and other published data	Howell et al. 2005; Baum et al. 2002; Le et al. 2002; Wilner et al. 1997; Komoike et al. 2006; Schmoor et al. 2000; Doyle et al. 2001; Lee et al. 2002; Kamby and Sengelov 1997;	DFS	ATAC trial; Howell et al. 2005	not a CUA	not a CUA

Study	Level of evidence of clinical data	Source of probabilities for recurrence/disease states	Efficacy estimates	Source of probabilities for adverse events	Utility weights	Source of utility weights
Thomas et al. (2009)	Trial (ATAC, ARNO) and published CEA studies	Forbes et al. 2008; Baum et al. 2002; Boccardo et al. 2005; Mansel et al. 2007	DFS	ATAC trial (absolute difference in DFS); Forbes et al. 2008	not a CUA	not a CUA
Lee et al. (2010)	Trial (ATAC) and other published data	ATAC trial (Howell et al. 2005, Baum et al. 2003 and 2002); EBCTCG 1998; Moran et al. 2002; Doyle at al. 2001; Haylock et al. 200; Schmoor et al. 200; Kamby and Sengelov 1997; Borner et al. 1994; Toonkel et al. 1983; Koning and Hart 1998	DFS	ATAC trials, BIG 1-98 trial (BIG 1-98 2005, 2009) and NSABP P-1 trial (Fisher et al. 2005)	Not reported	Sorensen et al. 2004; Mansel et al. 2007
Lux et al. (2010)	Trial (ATAC) and other published data	ATAC trialist group 2008; Kamby and Sengelov 1997, Moran and Haffty 2002, Stockler et al. 2000;Stockler et al. 2000, Roberts and Goldacre 2003, Raunes et al. 2001	DFS,TTR	ATAC 2005,2006, Icks et al. 2004, 2008 (for hip fractures)	DF, no AEs: 0.965 Common AEs (TAM): 0.956 Common AEs (anastrozole): 0.958 Vaginal bleeding: 0.926 Wrist fracture: 0.852 Local/regional recurrence: 0.766 HT for DR: 0.642 Endometrial cancer: 0.839 Spine fracture: 0.751 New CL BC: 0.702 DVT: 0.729 PE: 0.741 Hip fracture: 0.664 Chemotherapy for DR: 0.288 Current health: 0.893 MI: 0.750	Sorensen et al. 2004; Tengs and Wallace 2000; Sculpher, Manca and Abbott 2004;

Study	Level of evidence of clinical data	Source of probabilities for recurrence/disease states	Efficacy estimates	Source of probabilities for adverse events	Utility weights	Source of utility weights
					Stroke: 0.707 Hysterectomy: 0.899	
Yang et al. (2010)	Prospective observational studies	Korean breast cancer society registry	Overall survival	EBCTCG 1998	NA	not a CUA
Lux et al. (2011)	Trial (ATAC and BIG 1-98) and other sources	ATAC 2008; EBCTCG 1998; Thurlimmann et al. 2005; Mouridsen et al. 2009; Regan et al. 2009	Overall survival	Lux et al. 2010; Sorensen et al. 2004	**Disease situation (median)** DF during follow-up with status post BC: 75.0 Recurrent BC: 71.5 Metastatic BC: 70.0 Recurrent and metastatic BC: 69.0 Metastatic BC, chemotherapy: 58,0 Metastatic BC, ET: 70.0 Primary disease endometrial carcinoma: 60.0 **Adverse Events (mean)** No event: 0.974 Weight gain, hot flushes, vaginal, discharge: 0.963 Weight gain, limb pain, hot flushes, dryness of vagina: 0.959 DVT in legs: 0.796 Hip fracture: 0.730	Lux et al. 2010 (country specific using a visual analogue scale to derive health utilities from 600 women receiving treatment in Germany); Sorensen et al. 2004
Shih et al. (2012)	Trial (ATAC) and previously published CEA studies	Cuzick et al. 2010; Howell et al. 2005; Rocchi and Verma 2006; Mooremans et al. 2006	DFS	Mooremans et al. 2006	**No recurrence** No side effect 0.860 Hip fracture: 0.482 Wrist fracture: 0.475 Spine fracture: 0.372 Vaginal bleeding: 0.704 DVT: 0.554 PE: 0.329 Cataract: 0.519	A country specific study interviewing 20 oncology nurses using a developed tool

Study	Level of evidence of clinical data	Source of probabilities for recurrence/disease states	Efficacy estimates	Source of probabilities for adverse events	Utility weights	Source of utility weights
					Ischemic cerebrovascular events: 0.256 Musculoskeletal disorder: 0.629 Hot flushes: 0.730 Endometrial cancer: 0.472 **Loco-regional recurrence** New CL BC: 0.468 No side-effects: 0.491 General side-effects: 0.473 **Distant recurrence** No side-effects: 0.400 Side-effects from CT: 0.365 Side-effects from HT: 0.370	

Abbreviations: ARNO: Antithrombotic Regimens aNd Outcome, ATAC: Arimidex, Tamoxifen, Alone or in Combination, BIG: Breast International Group, disease-free, CEA: cost effectiveness analysis, CUA: cost utility analysis, DFS: disease-free survival, DR: distant recurrence, EBCTCG: Early Breast Cancer Trialist Collaborative Group, PFS: progression-free survival,TTP: time to progression, TTR: time to recurrence

Table 11-9: Estimation of resource use and costs – studies reviewed on economic evaluation of tamoxifen

Study	Source of resource use	Source of cost data	Costs included			
			Management of health events/states	Monitoring and treatment of AEs	Diagnostics	Others
Dranitsaris, Verma and Trudeau (2003)	Not reported	A Canadian hospital database	Hormonal drugs, hospitalisation, outpatient clinic visits, patient monitoring, administering drug, physician costs, chemotherapy	AEs monitoring and treatment costs included	Laboratory tests for management of events included	Pain medications

Study	Source of resource use	Source of cost data	Costs included			
			Management of health events/states	**Monitoring and treatment of AEs**	**Diagnostics**	**Others**
Simons, Jones and Buzdar (2003)	From literature; Bonneterre et. al. 2000	Insurance/payer company database	Hospitalisation, outpatient services, radiotherapy, surgical procedures, hormonal therapies, chemotherapy	AEs treatment costs included	Not reported	
Hillner (2004)	Not reported	Medicare payments (for costs associated endpoints such as local recurrence), published literature (other costs of treatment), but with US unit costs	Hormonal drugs, chemotherapy, radiotherapy, breast conserving surgery, mastectomy	Treatment costs included	Not reported	
Gil et al. (2006)	Local standard treatment guidelines	Spanish healthcare costs database; DRG or patient management categories	Primary care service, mastectomy, post-surgery admission, chemotherapy administration, radiotherapy, oncology visits, hormonal drug	Monitoring and treatment costs included	X-rays, ultrasound and CT scan, laboratory tests (e.g. tumour antigens liver and kidney functions)	
Lonning (2006)	Some resource use was reported to be approximated from local and other published literature source	Norwegian health system, retail price for drugs	Hormonal drugs	Not reported for baseline analysis, was reported for the SA	Not reported	
Moeremans and Annemans (2006)	Clinical expert opinion was used to validate an old study that used chart review to establish resource use	Local unit costs	Hormonal drugs	Treatment costs included	Not reported	
Rocchi and Verma (2006)	Expert panel composed of seven oncologist, Statistics Canada	Local unit costs, Ontario health insurance plan schedule and Ontario	Routine care, chemotherapy, radiotherapy, hormonal therapy	Monitoring and treatment costs included	Laboratory tests and procedures	Hysterectomy, bisphosphonates for 25% of

Study	Source of resource use	Source of cost data	Costs included			
			Management of health events/states	**Monitoring and treatment of AEs**	**Diagnostics**	**Others**
	population health model, and standard treatment guidelines	case costing initiative, treatment costs for rare adverse events and prices for chemotherapy visits and radiotherapy fractions from the literature (costs inflated to 2004 Can$)				patients in accordance to clinical practice
Locker et al. (2007)	Expert opinion from nine practising oncologists and members of the ATAC steering committee, and published literature	Unit costs were derived from standard US sources and published literature	Medical management, treatment of recurrence, palliative care	Monitoring and treatment costs included	Bone density scans, endometrial cancer monitoring	Hysterectomy
Mansel et al. (2007)	Expert panel and published literature (for treatment of adverse events)	Published sources, UK database (NHS reference cost, BNF (2003/2004)	Medical management during treatment and follow-up, management of disease recurrence	Treatment costs included	Not reported	Herceptin/month for the treatment of cancer recurrence
Skedgel et al. (2007a)	Not reported	Local unit cost, cost of treatment from local published literature and adjusted for inflation	Hormone therapy, long-term follow-ups, management of breast cancer relapses	Treatment costs included	Not reported	Herceptin therapy for HER2 positive patients with distant recurrence
Skedgel et al. (2007b)	Not reported	Local unit cost, wholesale acquisition cost for hormonal drugs, cost of treatment from local published	Hormone acquisition costs, hormone treatment and follow-up, and management of breast cancer relapse	Treatment costs included	Not reported	

Study	Source of resource use	Source of cost data	Costs included			
			Management of health events/states	**Monitoring and treatment of AEs**	**Diagnostics**	**Others**
		literature and adjusted for inflation				
Younis et al. (2007)	Not reported	Local unit cost, average wholesale price of hormonal drugs in the country, cost of treatment from local published literature and adjusted for inflation	Hormone acquisition costs, hormone treatment and follow-up, and management of breast cancer relapse	Treatment costs not included in baseline analysis, but included in the SA	Not reported	
Karnon, Delea and Barghout (2008)	Country specific; estimated from National Health Service (NHS) and the British national formulary	Unit costs from NHS, cost data from hospital database, costs of AES from published literature that described costs in local currency	Annual oncology outpatient visits, surveillance, costs of adjuvant therapies, surgical episodes, radiotherapy, chemotherapy, inpatient visits	Treatment costs included in baseline analysis but monitoring costs (bone mineral density screening) included in only the SA	Bone mineral density screening included only in SA	
Fonseca, Araujo and Saad (2009)	Modified Delphi panel consisting of Brazilian specialists	Local costs	Micro costing to estimate the cost of breast cancer treatment for the different health states	Not reported	Not reported	
Thomas et al. (2009)	Chart review	Local costs; UK hospital	Outpatient activity, oncology drugs, radiology, radiotherapy, GP visits	Not reported	Blood tests investigations	
Lee et al. (2010)	Clinical practice guideline for breast cancer in the country	List of fee schedule for the HTA agency and national health insurance statistical yearbook of the country	Hormonal drug costs, pharmacy fees, cost of hormonal therapy; doctor visit, transportation, treatment cost, monitoring breast cancer events	Treatment costs included	Diagnosing HR status	

Study	Source of resource use	Source of cost data	Costs included			
			Management of health events/states	Monitoring and treatment of AEs	Diagnostics	Others
Lux et al. (2010)	Expert opinion and published literature	National unit cost; German-DRG 2008 and EBM 2000plus	Costs of recurrence, follow-up costs, hormonal drug costs	Monitoring and treatment costs included	Yes; was reported to be included	Initial treatment costs of breast cancer before initiating hormonal therapy, indirect costs
Yang et al. (2010)	Korea breast cancer registry and standard treatment guidelines in Korea	National unit cost; Korea medical insurance charges	Costs of breast cancer events, costs of drugs	Monitoring and treatment costs included	Sonogram	
Lux et al. (2011)	Expert panel opinion	National unit cost; German-DRG, pharmacists prices in 2010	Costs of care, diagnosis and treatment (inpatient and outpatient costs)	Monitoring and treatment costs included	Vaginal USG and dual energy X-ray absorptiometry Laboratory and scans	
Shih et al. (2012)	Retrospective patient record review	Unit costs from Singapore hospital codes	Consultation fees, procedures, hospitalisation	Monitoring and treatment costs included	Laboratory and scans	

Abbreviations: AEs: adverse events, ATAC, BNF: British National Formulary, CT: computer tomography, DRG: diagnosis related group, HR: hormone therapy, GP: general physician, HER2: human epidermal growth factor receptor 2, NHS: National Health Service, SA: sensitivity analysis, USG: ultrasonography

11.6 Appendix 6: HTA in Ghana: Economic evaluation of tamoxifen for the hormonal treatment of early and advanced breast cancers among pre- and peri-menopausal women

Table 11-10: CHEERS statement

Section/item	Item no	Recommendations for reporting	Reported in section in Chapters	
			EBC model (Chapter 7)	ABC model (Chapter 8)
Title and abstract				
Title	1	Identify the study as an economic evaluation or use more specific terms such as 'cost effectiveness analysis', and describe the interventions compared.		
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.		
Introduction				
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Section 6.2 Section 7.1	Section 6.2 Section 8.1
Methods				
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Section 6.2 Section 7.1	Section 6.2 Section 8.1
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Section 6.2	Section 6.2
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Section 7.2.1	Section 8.2.1
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Section 6.2	Section 6.2
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Section 7.2.1	Section 8.2.1
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Section 7.2.4	Section 8.2.3
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Section 6.5.2 Section 7.2.3	Section 6.5.2 Section 8.2.3

Section/item	Item no	Recommendations for reporting	Reported in section in Chapters	
			EBC model (Chapter 7)	**ABC model (Chapter 8)**
Measurement of effectiveness	11a	Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.		
	11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Section 6.5.1 Section 7.2.3	Section 6.5.1 Section 8.2.3
Measurement and valuation of preference-based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Not applicable	Not applicable
Estimating resources and costs	13a	Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.		
	13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Section 6.5.3 Section 7.2.3	Section 6.5.3 Section 8.2.3
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Section 6.5.4 Section 7.2.3	Section 6.5.4 Section 8.2.3
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Section 7.2.1	Section 8.2.1 Section 7.2.1
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Section 7.2.1 Section 7.2.2	Section 8.2.1 Section 8.2.2
Analytic methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Section 7.2.3	Section 8.2.3
Results				

Section/item	Item no	Recommendations for reporting	Reported in section in Chapters	
			EBC model (Chapter 7)	**ABC model (Chapter 8)**
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Section 7.2.3 Section 7.2.5	Section 8.2.3 Section 8.2.5
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost effectiveness ratios.	Section 7.3.1	Section 8.3.1
Characterising uncertainty	20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).		
	20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Section 7.2.5	Section 8.2.4
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Section 7.2.5	Section 8.2.4
Discussion				
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Section 7.4	Section 8.4
Other				
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	The research for this thesis is supported by the Australian government International Research Training Program scholarship	
Conflict of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	None	

Table 11-11: Variables used in estimating DALYs averted

	Tamoxifen				**No tamoxifen**			
	HR	MST (months)	IHR	MTP	HR	MST (months)	IHR	MTP
Progression-free survival	0.011	66	0.012	0.010	0.013	51.61	0.013	0.013
Survival after progression	0.026	27.1	0.026	0.025	0.033	21.19	0.033	0.032
Overall survival	0.021	33	0.021	0.021	0.027	25.81	0.027	0.027

The MST for the tamoxifen arm was provided in the RCT findings while that for the no tamoxifen arm was estimated using the formulae provided in the main text. Refer to main text for formulae used to derive all other estimates. Abbreviation: HR: hazard rate, IHR: instantaneous hazard rate, MST: median survival time, MTP: monthly transition probability

Table 11-12: Estimating efficacy values for advanced breast cancer model

Health state	Age	LE	DYLLs	DYLDs	Disability weight	Duration of morbidity	DALYs	No. of deaths	Deaths averted	Total DALYs	DALYs averted
Advanced breast cancer											
Tamoxifen arm											
Pre-progression	50	74.3	29.75	3.85	0.41	11	33.59	0.027	0.027	0.00	0.91
Progression	51	74.3	29.75	5.06	0.54	11	34.80	0.032	0.007	0.87	0.24
No Tamoxifen arm											
Pre-progression	50	74.3	29.75	3.85	0.41	11	33.59	0.000	0.027	0.00	0.91
Progression	51	74.3	29.75	5.06	0.54	11	34.80	0.032	0.00	1.11	0.00
Early breast cancer											
Tamoxifen arm											
Disease-free with no recurrence	49	73.40	29.65	0.49	0.05	12.00	30.14	0.00	0.07	0.00	0.87
Contralateral breast cancer (CLBC)	50	74.30	29.75	1.81	0.29	7.00	31.56	0.02	0.01	0.63	0.28
Loco-regional recurrence (LRR)	50	74.30	29.75	2.05	0.32	7.00	31.79	0.02	0.01	0.64	0.29
Distant recurrence (DR)	50	74.30	29.75	4.22	0.45	11.00	33.97	0.02	0.01	0.68	0.31
Recurrence (LRR and DR)	50	74.30	29.75	3.99	0.43	11.00	33.73	0.02	0.01	0.67	0.30
Recurrence (CLBC, LRR and DR)	50	74.30	29.75	3.90	0.42	11.00	33.65	0.02	0.01	0.67	0.30
No Tamoxifen arm											
Disease-free with no recurrence	49	73.40	29.65	0.49	0.05	12.00	30.14	0.03	0.00	0.00	0.87
Contralateral breast cancer (CLBC)	50	74.30	29.75	1.81	0.29	7.00	31.56	0.03	0.00	0.92	0.00
Loco-regional recurrence (LRR)	50	74.30	29.75	2.05	0.32	7.00	31.79	0.03	0.00	0.92	0.00
Distant recurrence (DR)	50	74.30	29.75	4.22	0.45	11.00	33.97	0.03	0.00	0.99	0.00
Recurrence (LRR and DR)	50	74.30	29.75	3.99	0.43	11.00	33.73	0.03	0.00	0.98	0.00
Recurrence (CLBC, LRR and DR)	50	74.30	29.75	3.90	0.42	11.00	33.65	0.03	0.00	0.98	0.00

Abbreviations: DALYs: Disability adjusted life years, DYLDs: Discounted years lived with a disability (morbidity), DYLLs: Discounted years of life lost (mortality), LE: life expectancy at age, No.: number. Deaths averted = Number of deaths in no tamoxifen arm (0.0685)-Number of deaths in the tamoxifen arm (0.0543), Total DALYs = DALYs X number of deaths, DALYs averted = DALYs X deaths averted

11.7 Appendix 7: HTA in Ghana: Budget impact analysis of tamoxifen for the hormonal treatment of early and advanced breast cancers among pre- and peri-menopausal women

Table 11-13: Univariate and scenario sensitivity analysis for BIA

Description	Year 1 (GHC (AUD$))	Year 2 (GHC (AUD$))	Year 3 (GHC (AUD$))	Year 4 (GHC (AUD$))	Year 5 (GHC (AUD$))
NHIS coverage					
100% NHIS coverage	1,650,372.93 (478,608.15)	1,686,351.06 (489,041.81)	1,722,607.61 (499,556.21)	1,759,643.68 (510,296.67)	1,797,476.02 (521,268.04)
90% NHIS coverage	1,485,335.64 (430,747.34)	1,517,715.96 (440,137.63)	1,550,346.85 (449,600.59)	1,583,679.31 (459,267.00)	1,617,728.41 (469,141.24)
80% NHIS coverage	1,320,298.35 (382,886.52)	1,349,080.85 (391,233.45)	1,378,086.09 (399,644.97)	1,407,714.94 (408,237.33)	1,437,980.81 (417,014.44)
70% NHIS coverage	1,155,261.05 (335,025.71)	1,180,445.75 (342,329.27)	1,205,825.33 (349,689.35)	1,231,750.57 (357,207.67)	1,258,233.21 (364,887.63)
60% NHIS coverage	990,223.76 (287,164.89)	1,011,810.64 (293,425.09)	1,033,564.57 (299,733.72)	1,055,786.21 (306,178.00)	1,078,485.61 (312,760.83)
50% NHIS coverage	825,186.47 (239,304.08)	843,175.53 (244,520.90)	861,303.81 (249,778.10)	879,821.84 (255,148.33)	898,738.01 (260,634.02)
100% NHIS coverage and market price of tamoxifen	2,434,891.48 (706,118.53)	2,487,972.11 (721,511.91)	2,541,463.51 (737,024.42)	2,596,104.98 (752,870.44)	2,651,921.23 (769,057.16)
90% NHIS coverage and market price of tamoxifen	2,191,402.33 (635,506.68)	2,239,174.90 (649,360.72)	2,287,317.16 (663,321.98)	2,336,494.48 (677,583.40)	2,386,729.11 (692,151.44)
80% NHIS coverage and market price of tamoxifen	1,947,913.18 (564,894.82)	1,990,377.69 (577,209.53)	2,033,170.81 (589,619.53)	2,076,883.98 (602,296.35)	2,121,536.99 (615,245.73)
70% NHIS coverage and market price of tamoxifen	1,704,424.03 (494,282.97)	1,741,580.48 (505,058.34)	1,779,024.46 (515,917.09)	1,817,273.48 (527,009.31)	1,856,344.86 (538,340.01)
60% NHIS coverage and market price of tamoxifen	1,460,934.89 (423,671.12)	1,492,783.27 (432,907.15)	1,524,878.11 (442,214.65)	1,557,662.99 (451,722.27)	1,591,152.74 (461,434.29)
50% NHIS coverage and market price of tamoxifen	1,217,445.74 (353,059.26)	1,243,986.05 (360,755.96)	1,270,731.75 (368,512.21)	1,298,052.49 (376,435.22)	1,325,960.62 (384,528.58)
Proportions of early and advanced breast cancer for the current NHIS reimbursement price of tamoxifen					
Early:Advanced (50%/50%)	645,658.98 (187,241.11)	659,734.35 (191,322.96)	673,918.64 (195,436.40)	688,407.89 (199,638.29)	703,208.66 (203,930.51)
Early:Advanced (67%/33%)	654,653.08 (189,849.39)	668,924.52 (193,988.11)	683,306.40 (198,158.86)	697,997.49 (202,419.27)	713,004.43 (206,771.29)
Early:Advanced (80%/20%)	661,530.93 (191,843.97)	675,952.30 (196,026.17)	690,485.28 (200,240.73)	705,330.71 (204,545.91)	720,495.32 (208,943.64)
Proportions of early and advanced breast cancer for the current market price of tamoxifen					
Early:Advanced (50%/50%)	943,776.03 (273,695.05)	964,350.35 (279,661.60)	985,083.88 (285,674.32)	1,006,263.18 (291,816.32)	1,027,897.84 (298,090.37)
Early:Advanced (67%/33%)	952,770.13 (276,303.34)	973,540.52 (282,326.75)	994,471.64 (288,396.78)	1,015,852.78 (294,597.31)	1,037,693.62 (300,931.15)
Early:Advanced (80%/20%)	959,647.97 (278,297.91)	980,568.30 (284,364.81)	1,001,650.52 (290,478.65)	1,023,186.00 (296,723.94)	1,045,184.50 (303,103.51)
Cost of tamoxifen					
20% decrease	538,151.55 (156,063.95)	549,883.26 (159,466.14)	561,705.75 (162,894.67)	573,782.42 (166,396.90)	586,118.74 (169,974.44)

Description	Year 1 (GHC (AUD$))	Year 2 (GHC (AUD$))	Year 3 (GHC (AUD$))	Year 4 (GHC (AUD$))	Year 5 (GHC (AUD$))
40% decrease	449,161.39 (130,256.80)	458,953.11 (133,096.40)	468,820.60 (135,957.97)	478,900.24 (138,881.07)	489,196.60 (141,867.01)
50% decrease	404,666.31 (117,353.23)	413,488.03 (119,911.53)	422,378.03 (122,489.63)	431,459.15 (125,123.15)	440,735.53 (127,813.30)
53% decrease	391,317.78 (113,482.16)	399,848.51 (115,956.07)	408,445.25 (118,449.12)	417,226.83 (120,995.78)	426,197.20 (123,597.19)
67% decrease	329,024.67 (95,417.15)	336,197.41 (97,497.25)	343,425.65 (99,593.44)	350,809.30 (101,734.70)	358,351.70 (103,921.99)
70% decrease	315,676.15 (91,546.08)	322,557.89 (93,541.79)	329,492.88 (95,552.94)	336,576.98 (97,607.32)	343,813.38 (99,705.88)
80% decrease	271,181.06 (78,642.51)	277,092.81 (80,356.92)	283,050.31 (82,084.59)	289,135.89 (83,849.41)	295,352.31 (85,652.17)
100% decrease	182,190.90 (52,835.36)	186,162.66 (53,987.17)	190,165.16 (55,147.90)	194,253.71 (56,333.58)	198,430.17 (57,544.75)
20% increase	716,131.88 (207,678.24)	731,743.55 (212,205.63)	747,476.04 (216,768.05)	763,546.77 (221,428.56)	779,963.03 (226,189.28)
40% increase	805,122.04 (233,485.39)	822,673.70 (238,575.37)	840,361.19 (243,704.74)	858,428.95 (248,944.40)	876,885.17 (254,296.70)
50% increase	849,617.12 (246,388.97)	868,138.78 (251,760.24)	886,803.76 (257,173.09)	905,870.04 (262,702.31)	925,346.25 (268,350.41)
53% increase	862,965.65 (250,260.04)	881,778.30 (255,715.71)	900,736.53 (261,213.59)	920,102.37 (266,829.69)	939,884.57 (272,566.52)
67% increase	925,258.76 (268,325.04)	945,429.40 (274,174.53)	965,756.13 (280,069.28)	986,519.89 (286,090.77)	1,007,730.07 (292,241.72)
70% increase	938,607.28 (272,196.11)	959,068.92 (278,129.99)	979,688.91 (284,109.78)	1,000,752.22 (290,218.14)	1,022,268.39 (296,457.83)
80% increase	983,102.37 (285,099.69)	1,004,534.00 (291,314.86)	1,026,131.48 (297,578.13)	1,048,193.31 (303,976.06)	1,070,729.46 (310,511.54)
100% increase	1,072,092.53 (310,906.83)	1,095,464.15 (317,684.60)	1,119,016.63 (324,514.82)	1,143,075.48 (331,491.89)	1,167,651.61 (338,618.97)
Cost of follow-up visits					
10% increase	633,225.96 (183,635.53)	647,030.29 (187,638.78)	660,941.44 (191,673.02)	675,151.68 (195,793.99)	689,667.44 (200,003.56)
20% increase	639,310.21 (185,399.96)	653,247.17 (189,441.68)	667,291.98 (193,514.67)	681,638.76 (197,675.24)	696,293.99 (201,925.26)
30% increase	645,394.45 (187,164.39)	659,464.05 (191,244.57)	673,642.53 (195,356.33)	688,125.84 (199,556.49)	702,920.55 (203,846.96)
50% increase	657,562.94 (190,693.25)	671,897.81 (194,850.37)	686,343.62 (199,039.65)	701,100.00 (203,319.00)	716,173.65 (207,690.36)
60% increase	663,647.19 (192,457.68)	678,114.70 (196,653.26)	692,694.16 (200,881.31)	707,587.09 (205,200.25)	722,800.21 (209,612.06)
100% increase	687,984.17 (199,515.41)	702,982.22 (203,864.84)	718,096.34 (208,247.94)	733,535.41 (212,725.27)	749,306.42 (217,298.86)
10% decrease	621,057.47 (180,106.67)	634,596.52 (184,032.99)	648,240.35 (187,989.70)	662,177.52 (192,031.48)	676,414.33 (196,160.16)
20% decrease	614,973.22 (178,342.24)	628,379.64 (182,230.10)	641,889.80 (186,148.04)	655,690.43 (190,150.23)	669,787.78 (194,238.46)
30% decrease	608,888.98 (176,577.80)	622,162.76 (180,427.20)	635,539.26 (184,306.38)	649,203.35 (188,268.97)	663,161.22 (192,316.76)
50% decrease	596,720.49 (173,048.94)	609,729.00 (176,821.41)	622,838.17 (180,623.07)	636,229.19 (184,506.47)	649,908.12 (188,473.35)
60% decrease	590,636.24	603,512.11	616,487.62	629,742.11	643,281.56

Description	Year 1 (GHC (AUD$))	Year 2 (GHC (AUD$))	Year 3 (GHC (AUD$))	Year 4 (GHC (AUD$))	Year 5 (GHC (AUD$))
	(171,284.51)	(175,018.51)	(178,781.41)	(182,625.21)	(186,551.65)
	566,299.26	578,644.59	591,085.45	603,793.78	616,775.35
100% decrease	(164,226.79)	(167,806.93)	(171,414.78)	(175,100.20)	(178,864.85)
Cost of calcium tablets					
	622,692.21	636,266.90	649,946.64	663,920.49	678,194.78
10% decrease	(180,580.74)	(184,517.40)	(188,484.52)	(192,536.94)	(196,676.49)
	618,242.70	631,720.39	645,302.38	659,176.38	673,348.67
20% decrease	(179,290.38)	(183,198.91)	(187,137.69)	(191,161.15)	(195,271.11)
	613,793.19	627,173.88	640,658.12	654,432.27	668,502.56
30% decrease	(178,000.03)	(181,880.43)	(185,790.86)	(189,785.36)	(193,865.74)
	604,894.17	618,080.87	631,369.61	644,944.05	658,810.35
50% decrease	(175,419.31)	(179,243.45)	(183,097.19)	(187,033.78)	(191,055.00)
	631,591.22	645,359.91	659,235.15	673,408.71	687,886.99
10% increase	(183,161.45)	(187,154.37)	(191,178.19)	(195,288.52)	(199,487.23)
	636,040.73	649,906.42	663,879.41	678,152.81	692,733.10
20% increase	(184,451.81)	(188,472.86)	(192,525.03)	(196,664.32)	(200,892.60)
	640,490.24	654,452.93	668,523.66	682,896.92	697,579.21
30% increase	(185,742.17)	(189,791.35)	(193,871.86)	(198,040.11)	(202,297.97)
	649,389.26	663,545.94	677,812.18	692,385.14	707,271.42
50% increase	(188,322.88)	(192,428.32)	(196,565.53)	(200,791.69)	(205,108.71)

Note: Costs are presented in GHC (AUD$). AUD: Australian dollars, GHC; Ghana cedis. 1 GHC is equivalent to 0.29 AUD.

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